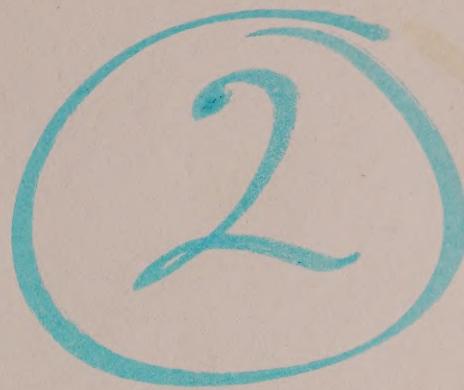


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ROYAL COMMISSION OF INQUIRY INTO CERTAIN
DEATHS AT THE HOSPITAL FOR SICK CHILDREN AND
RELATED MATTERS.

Hearing held in Court Room 20
Court House
361 University Avenue
Toronto, Ontario

The Honourable Mr. Justice S.G.M. Grange	Commissioner
P.S.A. Lamek, Q.C.	Counsel
E.A. Cronk	Associate Counsel
Thomas Millar	Administrator

Transcript of evidence
for
June 22nd, 1983

VOLUME 2

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1 ROYAL COMMISSION OF INQUIRY INTO CERTAIN
2 DEATHS AT THE HOSPITAL FOR SICK CHILDREN
AND RELATED MATTERS.

3

4 Hearing held in Court Room 20,
5 Court House, 361 University
6 Avenue, Toronto, Ontario, on
7 Wednesday, the 22nd day of June,
8 1983.

9

10 THE HONOURABLE MR. JUSTICE S.G.M. GRANGE - Commissioner
11 THOMAS MILLAR - Administrator
12 MURRAY R. ELLIOTT - Registrar

13

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20 I. J. ROLAND) for Sick Children
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14 F.J. SHANAHAN Mr. and Mrs. Inwood, Mr. and
15 W.T. TOBIAS Mrs. Turner, and Mr. and Mrs.
16 Lutes (parents of deceased
17 children)
18
19 VOLUME 2
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A/EMT/ak

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THE COMMISSIONER: I think it is most unlikely that Mr. Cimbura is going to be concerned about future prosecutions or future civil actions, but this applies to all witnesses, and I have been giving some thought to it.

If you look - you won't have these before you but I will tell you what is concerning me: Section 9 of the Public Inquiries Act says in Subsection 1 that a witness to an inquiry shall be deemed to have objected to answer any question asked him upon the ground that his answer may tend to criminate him or may tend to establish his liability to civil proceedings at the instance of the Crown, et cetera. And no answer given by a witness at an inquiry shall be used or be receivable in evidence against him in any trial or other proceedings against him thereafter taking place other than a prosecution for perjury in giving such evidence.

Now that - there is a constitutional problem as you may appreciate, and Subsection 2 says that a witness shall be informed by the Commission of his right to object to answer any question under Section 5 of the Canada Evidence Act.



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2

If you look at Subsection 5 of the
Canada Evidence Act which of course is a Federal
Statute, Subsection 1 is that no witness shall be
excused from answering any question upon the ground
of incrimination, et cetera, or liability to civil
proceedings.

7

And then Subsection 2, which is used
all the time, where a witness does object to answer
upon that ground, then the witness in those
circumstances - "...the answer so given shall not
be used or receivable in evidence against him in
any criminal trial or other criminal proceeding..."

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Now if that were all there was to it,
I would be obliged or somebody would be obliged to
say to every witness that Section 5 applies and
you can object on the grounds of incrimination,
and under those circumstances the evidence will not
be held against you.

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However, I take it the whole matter
is solved by Section 13 of the Charter of Rights
which says "A witness who testifies in any proceeding
has the right not to have any incriminating
evidence so given used to incriminate that witness in
any other proceedings, except in a prosecution for



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perjury or for the giving of contradictory evidence."

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Now I take the position, therefore,
that it is unnecessary to advise any witness of
Section 5 of the Canada Evidence Act, so I won't
do it.

5

6

Now I will hear argument if anybody
wants to argue me out of that position, and any
counsel is, of course, out of an abundance of
caution, is entitled to take any position with his
own client that he wants to. But as far as I am
concerned the witness is already protected under
the Charter of Rights and it is totally unnecessary.

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The next thing I want to say is
something about the transcripts.

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I understand that Mr. Chapman has
produced some and may have even distributed them
by now to those who are funded and to those who
are paying for them. I understand that in the
normal course they will be available the following
day. If for some reason you desperately want them
the night before to prepare yourself, I understand
they will be ready four or five hours after the
conclusion of the hearing at Mr. Chapman's office
if you seek them.

Now has anybody else anything before



1

2

Mr. Lamek starts in?

3

Yes, Mr. Ortved?

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MR. ORTVED: Just to follow up on
that order of business discussed at the latter part
of yesterday's proceeding, in connection with the
manuscript concerning the epidemiological assessment,
I have provided a copy of that to Mr. Lamek for you,
Mr. Commissioner, and I am given to understand -
my copy came to me via Dr. Carver, the Professor
of Pediatrics at the Hospital for Sick Children,
and it has been provided to them by one of the
authors who I understand is similarly one of the
authors of the Atlanta Report for comment.

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Apparently he checked with that

author and according to the letter which I have

given to Mr. Lamek, the author or one of them,

Mr. Buehler, takes the position because the

manuscript is in draft form and not final form he

has no objection to using it, Mr. Commissioner, but

feels it ought not to be distributed.

Now I leave that matter up to

Mr. Lamek and yourself.

THE COMMISSIONER: Anything on that,

Mr. Lamek?

MR. LAMEK: Mr. Commissioner,



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Mr. Ortved has indeed provided to me today a copy of the draft paper for publication together with a covering letter, and I am grateful to him for that. I have not had an opportunity to review it yet but on a close glance it appears to me - sort of quick glance - it appears to me to fall into the same category as the document that was referred to yesterday, the seven-page extract, and not to include the material which has been of concern, but I will confirm that on closer reading.

THE COMMISSIONER: Yes. All right.

Thank you.

Anything else?

All right then, Mr. Lamek, will you proceed?

MR. LAMEK: Thank you,
Mr. Commissioner.

May I call then Mr. George Cimbura?

GEORGE CIMBURA, Sworn

DIRECT EXAMINATION BY MR. LAMEK:

Q. Mr. Cimbura, if you prefer to stand or sit, it is entirely up to you.

A. Thank you.

Q. You are now I understand the Deputy Director of the Centre for Forensic Sciences



1

2 here in Toronto?

3 A. That is correct, sir.

4 Q. And when did you become
5 Deputy Director?

6 A. This was last year, in July
7 of last year.

8 Q. July of 1982. Prior to that
9 you were the head of the Toxicology Section of the
Centre for Forensic Sciences?

10 A. That is correct, sir.

11 Q. And you had been a member of
12 the Toxicology Section since 1961 I understand?

13 A. That is correct.

14 Q. Becoming the head of that
Section in 1968?

15 A. That is correct, sir.

16 Q. And will you just tell us
17 very briefly, if it is possible to do it briefly,
18 Mr. Cimbura, what is toxicology?

19 A. Well, forensic toxicology deals
20 with the examination of items received from various
21 criminal and medical-legal investigations for the
presence of alcohol, drugs and other chemical
22 poisons and the interpretation of the result of
23 findings in body specimens and related items with

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regard to their possible significance.

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Q. In terms of your educational background and qualifications, Mr. Cimbura,^{now} I quickly have it from you that you were graduated from the University of Toronto in 1959 with a Bachelor of Science Degree in Pharmacy.

8

A. That is correct, sir.

9

Q. You received the Master of Science Degree in Pharmacy from that same University in 1963?

10

A. That is correct, sir.

11

THE COMMISSIONER: Bachelor in 1969?

12

MR. LAMEK: Q. 1959 and Master of Science in 1963. By the time, therefore, you obtained your Master's Degree you were already employed as a member of the Toxicology Section of the Centre for Forensic Sciences?

13

A. That is correct, sir.

14

Q. You are a past President of the Canadian Society of Forensic Science?

15

A. That is correct.

16

Q. And past Chairman of the Toxicology Section of that Society?

17

A. That is correct, sir.

18

19



1

2 Q. And a Fellow of the American
3 Academy of Forensic Sciences?

4 A. That's correct.

5 Q. And a Member of the
6 International Society of Forensic Toxicologists?

7 A. That's right, sir.

8 Q. And also, much closer to home, you
9 are, I understand, a Member of the Drug Advisory
Committee for the Ontario College of Pharmacists?

10 A. That's correct, sir.

11 Q. And lest there be no misunder-
standing - lest there be any misunderstanding, Mr.
12 Cimbura, tell us, what is forensic science?

13 A. Forensic science provides
14 assistance by means of scientific analyses to various
15 official agencies involved in our system of
16 administration of justice. This would be agencies
17 such as police agencies, crown attorneys, defence
18 counsel, coroners, pathologists and other investigators
19 in various forms of scientific analyses.

20 Q. You told us what toxicology is,
21 Mr. Cimbura. I would take it that the analysis of
22 blood or tissues for the presence of drugs is carried
23 on in the toxicology section of the Centre for
24 Forensic Sciences?

25



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2 A. That's correct, sir.

3

Q. Is there any other section
of the Centre which carries on such analyses?

4

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A. No, this is done in our
Toxicology Section, that's correct, sir.

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Q. I know, Mr. Cimbura, that you
became involved in the analysis of blood and tissue
for digoxin in the late winter, early spring of
1981 with respect to samples that were received
at the Centre from children who had died in the
Hospital for Sick Children, that's so, isn't it?

A. Well, as I recollect, this
was in, yes, March, 1981, that's correct.

Q. Now, prior to that, had you
had any experience in digoxin analysis of samples?

A. Not really any substantial
degree of experience altogether, not in relation
to the more modern techniques that are involved
in digoxin analysis. I would say no, that's right.

Q. To your knowledge, had anyone
else in the Toxicology Centre had such experience
prior to the spring of 1981?

A. Well, perhaps if I could
modify my previous answers. I was generally
familiar with the drug digoxin and generally



1

2 familiar with the techniques used, but no personal
3 experience. There was no one else.

4

5 THE COMMISSIONER: Mr. Lamek, I'm
6 having a little problem, I don't know whether any-
7 one else is. I know you are speaking into the
8 machine. How is the hearing for Counsel generally?
9 It's probably only age that's the problem. All
10 right, we'll carry on, do the best you can.

11

12 MR. LAMEK: Q. You can make a
13 tune on those, Mr. Cimbura.

14

15 Can you tell us, please, does the
16 detection and measurement of digoxin in, let us say
17 blood, involve any particular problems? Are there
18 any qualities of digoxin that make its detection
19 and measurement difficult?

20

21 A. Well, yes, one characteristic
22 is that the doses of digoxin are relatively low,
23 it's a potent drug.

24

25 THE COMMISSIONER: I'm sorry, what
was that?

26

27 THE WITNESS: It's a potent drug.

28

29 THE COMMISSIONER: Yes, all right.

30

31 MR. LAMEK: Mr. Cimbura said the
32 doses are small, it is a potent drug.

33

34 THE WITNESS: With the result that

35

36



1

2 after distribution in the body the quantities to be
3 detected are extremely small. They are in, as we
4 measured them, nanograms per millilitre, one nano-
5 gram being one-billionth of a gram. This is one
6 potential problem with respect to analyses which
7 require certain techniques. Another potential
8 problem with respect to digoxin is that it has a
9 high molecular weight.

10 MR. LAMEK: Q. A high molecular
11 weight?

12 A. Molecular weight.

13 Q. What is the significance of
14 that?

15 A. Well, the significance I am
16 attempting to allude to is that, for example, one
17 of the instrumental techniques which has now become
18 very useful in forensic toxicology is mass
19 spectrometry coupled with gas liquid chromatography,
20 and because of the high molecular weight of digoxin
21 and other chemical aspects of digoxin, this
22 particular good technique does not lend itself
23 readily to digoxin analysis.

24 I'm not sure whether I've answered
25 your question.

Q. Yes, thank you.



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THE COMMISSIONER: You answered the question but it doesn't explain it to me. What is the high molecular weight and does it affect the analysis?

THE WITNESS: The particular instrumentation mass spectrometry coupled with gas chromatography lends itself more to analyses of lower molecular drugs than digoxin has. It provides the necessary separation on the column and the passage from the gas chromatography to the mass spectrometry.

MR. MANNING: I'm sorry, Mr. Commissioner, I can't hear, he's dropped his voice down.

THE COMMISSIONER: I know. The problem is he's trying to satisfy me by speaking to me and, as a result, he's speaking away from the microphone. So, it's a problem. Now, those two microphones, do they both perform the same service? There are three of them!

Yes, all right, carry on, Mr. Lamek.

MR. LAMEK: Q. Mr. Cimbura, do I understand the answer you just gave to the Commissioner that certain sophisticated analytical techniques and equipment is not appropriate for use for the analysis of digoxin simply because of the



1

2 size and the weight of the digoxin molecule? Is that
3 essentially what you are saying?

4

factors
5 parties that I mentioned, the low quantities present,
6 the large molecule and the water *solubility* of digoxin
7 and certain other chemical properties, that's right,
8 make it less readily applicable to -- I believe now
9 something happened to the microphones -- make it less
10 readily applicable to sophisticated instrumentation
11 such as mass spectrometry combined with gas liquid
chromotography.

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Q. For those reasons then, certain analytical techniques are not, I take it, available or suitable for use in the analysis of digoxin, but I take it from what you have said about the very small quantities of digoxin one may expect to find in blood, that the analytical techniques that are used are required to be extremely sensitive to detect very small quantities. Is that fair?

A. That's correct, sir.

Q. All right. Now, what, in 1981, was the analytical procedure that was used either at your lab or generally for the detection and measurement of digoxin in, let us say, blood?

A. Well, the most common procedure



1

2 at that time reported in the literature and I believe
3 used in clinical laboratories as well as some
4 forensic laboratories was the technique of radio-
5 immunoassay.

6

Q. Radioimmunoassay?

7

A. That's correct, sir.

8

Q. I believe that is commonly
referred to ~~in~~, and I will also refer to it as RIA?

9

A. That's correct, sir.

10

Q. Now, can you tell us please what
is the principle upon which that analytical technique
or procedure operates, how does radioimmunoassay
operate to detect and measure digoxin in blood, what's
the principle of it?

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A. The principle of this technique is based really on two principles. It is based on the principle of radioactive measurements --

Q. Radio?

A. Radioactive measurements.

MR. MARSHALL: I am sorry, radio -- ?

THE WITNESS: Radioactive measurements.

MR. LAMEK: Q. Radioactive measurements.

A. Yes, and the principle of immune response, immunology.

Q. Can we take those two separately for the moment, Mr. Cimbura? First you say radioactivity measurements. In units of the kinds that you have expressed, that is to say nanograms billions of a gram, I take it we are not weighing the substance so much as detecting it by other means. Is that what the radioactivity measurement element is about in this process?

A. Yes. If I may try to explain briefly.

Q. Yes.

A. In my own words. The essential complements of any radioimmunize technique are



1
2 first of all an antibody to digoxin. This anti-
3 body is produced in animals by injecting the animal
4 with a special form of the drug, in this case
5 digoxin, we are talking about, and collecting the
6 blood from the animals and subjecting it to various
7 purification processes and as a result one ends up
8 with an antibody to the drug digoxin.

9 The second essential complement is
10 a digoxin compound which is incorporated into a
11 radioactive label, so-called label, Mr. Commissioner.

12 Q. Label or tag.

13 A. In case of the radioimmuno-
14 assay we are using, and which is usually used,
15 the radioactive tag is iodine 125 which is
16 incorporated into the molecule of digoxin.

17 Those are two essential complements. There are
18 other complements, the so-called package or kit
19 that are in many cases commercially available for
20 laboratories.

21 The overall technique after mixing
22 various re-agents including the two complements I
23 have mentioned with the specimen for analysis under
24 control conditions, there is a competition during
25 the test between the radioactive digoxin and any
cold, if I may refer to the term, that is non-radioactive.



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Dr. M.D.

2

elements. A sample of blood which you want to
analyze, that is one, is it not?

4

A. That is correct.

5

Q. The second: digoxin which has
been tagged with a radioactive substance, you say,
generally iodine 125.

7

A. That is correct.

8

Q. And third: antibodies which as
you have told us are produced from the bodies of
animals, antibodies to digoxin.

11

A. That is correct.

12

Q. Can we just focus on those
antibodies for a moment. As I understand it and
I have a very feeble understanding of the principles
of immunology, but as I understand it if a substance
is introduced into the body, the body will manufacture
or produce bodies which will in effect neutralize
that body by seizing upon it. Is that a very rough
description?

19

A. Yes. I should qualify that.

20

I am not an expert in immunology myself.

21

Q. It is clear I am not,
Mr. Cimbura, but if we can have at least a basic
understanding.

23

A. That is a basic understanding,

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that is right.

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Q. And the antibody that the body produces, is if you will, rather like a sort of hand and glove situation. It is fitted to the shape of the substance which it wants to lock up and neutralize. Is that fair?

A. Yes, somewhat.

Q. And so if my left fist is the substance that has been introduced and it is a substance which my body does not particularly want to have, it will form an antibody in the shape of my right hand and the two will lock together and in effect the foreign body is going to be effectively neutralized. Is that the principle?

A. Yes, that is roughly the principle of an immune response in the body to the foreign material.

Q. And what you are obtaining, having been manufactured in the bodies of animals is an antibody which will seize upon the digoxin molecule?

A. That is correct.

Q. And so am I right that the antibody around its surface or whatever it may be has a number of sites which are capable of taking



1

2 up digoxin molecules?

3

A. That is right, so to speak.

4

5

6

7

Q. I have done it in a sort of one situation or illustration but in fact there would be a group of these to take up a group of these?

8

A. Yes, the actual sites are, I believe, known but this is roughly --

9

Q. That is the basic principle?

10

A. That is right, sir.

11

Q. Now, with these three elements, that is to say the sample to be analyzed and the radioactive tagged digoxin and the antibodies, you said when you put the three together, as you would in the assay, there is a competition between the radioactive tagged digoxin which you have introduced and any digoxin which may be present in the sample which you are analyzing?

12

A. That's right.

13

Q. Those two compete in a sense, not in any deliberate intentional way, but there is competition between them for sites on the antibody.

14

A. For the available sites.

15

Q. For the available sites?

16

A. That is right.

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Q. And by measuring the amount of radioactivity you are able to determine I take it by extrapolation of some kind either what number of sites in the antibody are taken up by digoxin from a sample and thence the concentration of digoxin in the blood. Is that a fair shortened summary of what happens?

A. Well, yes, actually when either the labelled digoxin or else the cold digoxin combines with the antibody, a so-called complex is formed and by different processes, depending on the radioimmunoassay that is being used, the complex clumps or forms a precipitate, if I may use the term, which can be suitably separated from the more fluid medium of the reaction mixture.



1

MT/ko 2 Q. Yes, I see.

3

A. And it is this precipitate which
4 is in our technique subjected to counting for gamma
radiation stemming from the *iodine* ~~125~~ 125.

5

Q. And when you speak of the
complex ~~compound~~ you are speaking of the antibody to which
6 there has now been bound either the radioactive tagged
7 or
8 digoxin/and digoxin from the sample itself?

9

A. That is correct, sir.

10

Q. And that you call a complex?

11

A. That is a complex which can be
physically separated from the reaction mixture.

12

Q. All right.

13

A. By suitable processes and
14 subjected to counting for gamma radiation.

15

Q. Now you referred to standards.

16

As I understood what you meant by that, you have
samples with known concentrations of digoxin in them,
and you are therefore able, by running those samples
through the process and seeing what the results are,
what the clumping is, and what the radioactivity is,
you are able therefore to say that degree of radio-
activity measurement represents this concentration,
the known concentration, that we put in. Is that
fair?

24

25



1

2 A. That is correct.

3

4 Q. And if you do that two or three
5 times with different known concentrations you are able
6 to calibrate in effect and therefore plot the actual
7 results on the actual sample along that linear graph
8 and make a determination of the concentration of
9 digoxin in the actual sample?

10

A. That is correct, sir, yes.

11

Q. All right. Now we have been
12 referring to the antibodies. Are the antibodies which
13 are used in this process, Mr. Cimbura, specific to
14 digoxin? That is to say is it only digoxin that they
15 will attract and bind?

16

A. No. I should say that all
17 analytical techniques have ^{the} advantages and disadvantages
18 of radioimmunoassay is that drugs or compounds
19 similar to digoxin, chemically similar to digoxin,
20 can cross-react with the radioimmunoassay..

21

Q. When you say chemically similar
22 to digoxin, do you mean similar in molecular structure?

23

A. That is correct, sir.

24

Q. Sufficiently similar that they
25 are --

26

A. Similar in chemical structure,
27 yes.

28



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Q. Sufficiently similar in chemical structure that they are able to bind with the digoxin antibody as well as digoxin itself?

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A. To a varying degree depending where they are, yes.

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Q. And therefore do I take it that the result of a radioimmunoassay is to record a level that may not be entirely digoxin but may also include certain other substances which because of their chemical similarity to digoxin may also have bound on the antibody and therefore have brought themselves into the measurement you talked about?

A. Yes. In theory this may happen.

Of course overall considering all the possibilities, known possibilities that could do this cross-reactivity, I still consider it a good screening test, let's say at a clinical setting where people know which drug is administered.

Q. Yes?

A. And therefore can be fairly sure that that is the drug they are measuring.

Q. You have used the term cross-reactivity. Are you using that term to describe the capacity of the antibody to attract not merely digoxin but substances chemically similar to digoxin?



1

2 A. That is correct.

3

Q. Substances other than digoxin
itself cross-react with the antibody? Is that what
we are saying?

4

A. That is right.

5

Q. Is it known, Mr. Cimbura, what
these digoxinlike substances are?

6

A. Well, there are a number of them
that have been described either in the various
commercially available kits for digoxin that one
purchases or else in the scientific literature in
general. They fall generally into two groups. One
group is the so-called metabolites of digoxin.

7

Q. Metabolites?

8

A. Metabolites, which I could
describe as breakdown products by the body of digoxin
after digoxin is administered. And I believe there
are about four of these that have been described.
Actually they have been both described and the cross-
reactivity also determined by our experimental work
at the Centre.

9

The other group of substances are some
drugs other than actually digoxin but chemically
similar to digoxin such as, for example, if I may
illustrate, drugs such as Lanatoside C.

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Q. I am sorry, could you say that

again?

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MR. STRATHY: It would be some help if
the witness could spell the substance.

5

MR. LAMEK: Q. Could you spell that
for us?

6

A. L-a-n-a-t-o-s-i-d-e C. Another
drug is deslanoside. It is spelled d-e-s-l-a-n-o-s-i-d-e.
Digitoxin as opposed to digoxin and --

7

10

THE COMMISSIONER: How do you sell
that?

11

12

THE WITNESS: D-i-g-i-t-o-x-i-n.

13

These drugs are chemically similar to digoxin.

14

MR. LAMEK: Q. Is it known, Mr.
Cimbura, whether any of those substances is manufactured
by the body? Is any of them endogenous, the ones you
have named?

15

16

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A. Well, certainly with respect to
digoxin itself I have not seen any published work which
would enable me to postulate that digoxin is produced
naturally in the body.

18

19

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I haven't seen anything with respect to
the other drugs that I mentioned as well. Of course,
as I mentioned previously, the metabolites or the
breakdown products of digoxin are produced in the body

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2 after digoxin is administered.

3

4 for those metabolites to be present and cross-reacting
5 with the antibody there would have to have been an
6 administration of digoxin to the patient at some prior
time?

7

A. That is correct.

8

9 Q. And you are not aware I think you
10 said of any literature to the effect that any of the
other drugs you mentioned as being similar to digoxin
11 is endogenous?

12

A. No, I haven't seen anything like
that. I would not expect them to be endogenous.

13

14

Q. Now, Mr. Cimbura, to the extent
15 that these other substances whether they be the
16 metabolites of digoxin that you referred to or these
17 other chemically similar drugs are capable of binding
18 with the antibodies that are used in the RIA, may
there be a distortion of the results of the RIA to
19 the extent that substances other than digoxin itself
are being measured?

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A. Yes, there may. In theory,

there may. I should perhaps mention that with respect
to digoxin and its metabolites, the extent of the
problem in practical terms does not appear to be



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2 substantial because digoxin is metabolized to a minor
3 extent, under general circumstances with some
4 exceptions in persons who are suffering from renal
5 failure where the metabolites can accumulate as a
6 result of the clinical condition to a larger
7 proportion than normal.

8

9 Q. Where there is normal renal
10 function any broken down or degraded or metabolite of
11 digoxin will be eliminated usually by the kidneys I
12 take it?

13

14 A. They will be eliminated and
15 their proportion normally would be relatively minor.

16

17 Q. The proportion remaining in the
18 blood?

19

20 A. Yes, that is right.

21

22 Q. Mr. Cimbura, is there a way, a
23 technique, a procedure, for isolating the true digoxin
24 from these other digoxin-like substances in a blood
Sample
cell?

25

26 A. Well, because of the limitation
27 of the radioimmunoassay that I mentioned previously -
28 we were just talking about it - this was my objective
29 in 1981 to evaluate and develop a technique which
30 could separate digoxin from the known interferences, yes.

31

32

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34

35

Q. I want to come back to that in a



1
2 moment, but can you tell us what that technique is
3 and then I will come back and have it described
4 later?

5 A. Oh, that technique basically
6 utilizes high pressure liquid chromatography equipment;
7 for short, HPLC.

8 THE COMMISSIONER: HPLC?

9 THE WITNESS: HPLC, Mr. Commissioner,
10 for the separation process, and in our hands another
11 RIA then is employed as a detector following the
12 separation by HPLC.

13 MR. LAMEK: Q. All right. Now as I
14 say I want to come back to that process and technique
15 in a moment, but there is a technique available which
16 can - can I put it this way? - refine the sample that
you want to analyze by extracting from it the digoxin
and not the other digoxinlike substances?

17 A. That is right.

18 Q. All right. And you may then take
19 the refined sample free of the known digoxinlike
20 substances and run that through your radioimmuno-
assay procedure?

21 A. That is correct, sir.

22 Q. As I say I want to come back to
23 that.

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Could you tell us please, Mr. Cimbura,
where do you obtain the radioactive digoxin that you
use in the RIA at the Centre?

5

6

A. Yes. We obtained that from
Beckman Company as a kit, as I mentioned, or package,
called RIA Phase.

7

8

Q. And that is from Beckman,
B-e-c-k-m-a-n, Company?

9

A. I believe so, yes.

10

11

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Q. And the kit consists of the
radioactive digoxin, the digoxin antibodies and what,
the standards as well?

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A. The standards.

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Q. The standards of known
concentration you used to calibrate the equipment?

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Q. Now, we have been speaking of the ~~IR~~ procedure to analyze for the presence of digoxin and the measurement of digoxin samples of blood. Is that assay run on whole blood, Mr. Cimbura? Let's speak first of anti-mortem sample, a sample taken from a living patient. Do you run this procedure on whole blood?

A. Well, I or we run it at the Centre. We run on, well, if we get serum, we would have to run it on serum, we couldn't get the whole blood, but if we do get the whole blood, we run it on whole blood after suitable preparation of the whole blood.

Q. What's involved in the preparation of blood?

A. What is involved is another ~~separate~~ ^{fin} process, not as extensive as the HPLC but it involves a so-called extraction. By extraction I mean that the whole blood matrix is mixed in suitable proportion with an organic solvent, specifically dichloro methane and the mixture shaken, and this is referred to as an extraction process in toxicology, the idea being that digoxin would tend to leave the matrix of the cells and the other biological matrix and because of its chemical



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nature would tend to go into the organic solvent layer which can be then collected and evaporated and then subjected to the radioimmunoassay.

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Q. All right. Mr. Cimbura, I used the term whole blood, by that I mean whatever it is they draw right out of wherever it is they draw it from, I mean, by vein or whatever. Is that whole blood as it comes direct from the body?

9

10

11

A. Yes, essentially whole blood is a mixture of red blood cells and the fluid components of the body.

12

13

14

Q. And you've told us of the extraction process to which you submit a whole blood sample in order to arrive ~~derive~~ at that component of the blood upon which you do the RIA?

15

16

A. I'm sorry, would you repeat your question.

17

18

19

Q. Yes. You've told us of the extraction process to which you submit a whole blood sample in order to produce the material upon which you will do the actual RIA procedure?

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21

A. In order to - I didn't get that word.

22

23

Q. In order to - you've told us how you deal with whole blood.

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A. Yes.

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Q. And get it down to that component

4 which goes into the RIA machine.

5

A. That's right, yes.

6

Q. Yes.

7

A. It's a purer component that
goes in free of the matrix of the whole blood.

8

Q. Sure. Mr. Cimbura, in the
9 analysis of anti-mortem blood samples, does it make
10 any difference from what point of the body the
11 blood was drawn?

12

A. Well, my experience does not
13 really extend to that much of analyses of specimens
14 taken from live patients. I would expect it would
not, once the drug is in equilibrium, in the body,
15 I would expect it would be taken from a peripheral
16 circulation such as a vein in the arm or so on.
17 Actually, I haven't seen any study which would
18 compare the different sites taken while the patient
19 is alive.

20

Q. You say once the drug is in
21 equilibrium it shouldn't matter from what point of
the body the blood is drawn in a living patient.
22 What do you mean by when the drug is in equilibrium?

23

THE COMMISSIONER: Excuse me just a

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2 moment, please. Yes, Mr. Scott?

3

4 MR. SCOTT: Mr. Commissioner, I
5 know we're in a background phase of the Inquiry.
6 I'm sure Mr. Cimbura will feel perfectly free to
7 say if the questions that Mr. Lamek asks really go
8 to the expertise of somebody else. I understand
9 what Mr. Cimbura is telling us, and I think my
10 friend is trying to get him to act like a
pharmacologist at the moment and I'm just a little
troubled about that.

11

12 THE COMMISSIONER: Well, he seems
13 to be careful about it. As you know, Mr. Scott,
14 we always, even in proper cases we allow a little
bit of leading on this sort of problem, but in an
inquiry, we can have as much as we like, but then
15 it goes to weight.

16

17 MR. SCOTT: Well, it's not leading
18 I object to, it's the question asked, was asked of
19 Mr. Cimbura, does it make any difference from what
part of the body you take the blood or the tissue
20 which is going to be sampled?

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THE COMMISSIONER: And your point is?

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MR. SCOTT: You're talking about
blood, not tissue. I presume the next question is
tissue?

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MR. LAMEK: Let Mr. Scott wait for
the next question, Mr. Commissioner. That's not the
next question, he's wrong.

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THE COMMISSIONER: Well, I note
what you say. I certainly will bear it in mind as
to weight that will be given to it. I'm finding
this helpful, the leading and the summary of the
evidence. If it's improper I expect you to tell me.

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MR. SCOTT: Well, that's what I'm
doing.

THE COMMISSIONER: Yes.

MR. SCOTT: The point I am making
is that Mr. Cimbura is an expert on this testing
mechanism and I presume that he's being asked about
that but the last question goes well beyond that.

THE COMMISSIONER: Yes, all right.

MR. LAMEK: Mr. Commissioner, I
have no wish to take Mr. Cimbura beyond the bounds of
his knowledge and expertise and I have no doubt if
Mr. Cimbura feels uncomfortable or not qualified to
answer the question he will say so. He used a term,
however, that was to say, if the drug has reached
equilibrium, or words to that effect, and I asked
him what that meant.

THE WITNESS: Equilibrium with



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respect to the distribution between blood and the
various tissues in the body.

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MR. LAMEK: I had better make sure
that my next question isn't about tissue, Mr. Scott.

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MR. ORTVED: I'm sorry, I didn't
get that answer.

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MR. LAMEK: I said I'm making
sure that my next question isn't about tissues,
Mr. Scott.

10

11

MR. ORTVED: I didn't get
Mr. Cimbura's answer to the previous question.

12

MR. LAMEK: Oh, okay.

13

14

Q. Could you tell us again what
you mean by when the drug has reached a state of
equilibrium?

15

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A. Yes, when the drug reaches
an equilibrium between the blood and the concentra-
tions in various tissues of the body.

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THE COMMISSIONER: I must say I'm
having some problem with that. But before I go into
it any more, bearing in mind Mr. Scott's objection,
what's your knowledge with respect to this question?

THE WITNESS: Well, with respect
to the original question, I haven't seen any studies,
Mr. Commissioner. I haven't seen anything described



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in the literature that would actually compare the --

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THE COMMISSIONER: Would you be concerned - I take it though that you would be given several samples of ante-mortem, before death blood to experiment on it to determine the quantity of digoxin, would you not?

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THE WITNESS: Yes.

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THE COMMISSIONER: You are nodding your head, I think you are nodding your head. I'm not asking you to tell us about them, were you given that in the course of your investigation?

12

THE WITNESS: Oh, yes.

13

THE COMMISSIONER: Yes. Did you concern yourself as to where the blood was taken from?

15

THE WITNESS: No, I did not concern myself with respect to blood taken from a live patient.

18

THE COMMISSIONER: Yes.

19

THE WITNESS: I would have concern with respect to blood taken from a dead patient.

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THE COMMISSIONER: Yes, all right, thank you.

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MR. LAMEK: Q. The question was, you will recall, Mr. Cimbura, count in terms of

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blood taken from a living person.

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A. That's right.

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Q. And your answer, as I recall it,

was that as long as the drug had reached a state of what you call equilibrium, which you had since explained for us, you would not be concerned to know from what part of the body the blood came?

A. Yes, that's right, assuming

that it came from an intact vein, which I would

assume it usually is taken from, or an intact

blood vessel, that's right.

Q. How long does the RIA procedure take to perform, Mr. Cimbura, from the moment you pick up your sample until the time you get a result?

A. The procedure has quite a few steps in it. One of the advantages of RIA is that it lends itself to analyses of a multiple amount of specimens at the same time. So that if I can approximate, let's say, doing the extraction and the radioimmunoassay on 10 specimens, it would take us, providing things are working properly and everything is under control, it should take us about one and a half to two days.

Q. To two days?

A. Yes.



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(Lamek)

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Q. Mr. Cimbura, how high --

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THE COMMISSIONER: I'm sorry, just so I understand. Is that for each sample?

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THE WITNESS: No, that's doing the 10 specimens at the same time, Mr. Commissioner.

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THE COMMISSIONER: All right.
THE WITNESS: It could probably be done somewhat of a shorter time but I'm talking about a reasonably comfortable time.

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THE COMMISSIONER: Right.

MR. LAMEK: Q. I'm not quite sure

then that I do understand the answer. Is the length of time, one and a half to two days, a function of the number of samples that you are testing?

A.

To a smaller extent, I think all the samples have to be taken through the same steps. So, to some extent it is a function of the number of samples but I think not to a major extent, that's why it lends itself to a relatively large number of samples at the same time as opposed to doing only one sample.

if,

Q. In other words, if to do 10 samples, it took eight hours of elapsed time, you couldn't do one sample in one-tenth of eight hours?



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2 A. No.

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Q. No.

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A. No.

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Q. Okay. Mr. Cimbura, how high
a level of digoxin can the RIA equipment measure?

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A. Well, it can measure very
7 high levels. Perhaps I should begin by saying that
8 the calibration curve which I have mentioned
9 previously, is calibrated between .5 nanograms per
10 millilitre and 6 nanograms per millilitre at the
11 upper scale.

12

Q. So, the scale runs from .5
13 nanograms to 6 nanograms per millilitre?

14

A. The calibrations are correct,
that is correct.

15

Q. Now, what happens if you are
16 analyzing a sample and the reading goes off the
17 high end of the scale, what do you do then?

18

A. Well, when the reading goes
off the calibration scale, the assay must be
19 repeated by probably dilutions of the sample in
20 order to bring whatever concentration is there to
21 the range on the calibration curve.

22

Q. All right, let me understand
23 that. Let's assume a sample of blood which is put
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through this entire process and at the end of this process, the level recorded - all you can tell is that it is higher than the top end of your scale, more than 6 nanograms per millilitre.

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A. Yes.

7

Q. You don't know how much higher than 6, do you, it could be 7 or it could be 107?

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A. That's right.

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Q. And, therefore, if I understand you correctly, you take I suppose more of that same sample and dilute it. Would you in the first place dilute it one to one?

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A. It is usual but it is somewhat different in our situation than any clinical situation I suppose where, you know there is a sort of an expected range of concentration that you might run into in our situation, especially on this type of investigation. We had no idea what the concentrations may be and, for that reason, so-called serial dilutions are performed at the same time.

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Q. Serial dilutions?

21

A. Serial dilutions.

22

Q. Yes.

23

A. That's right.

24

Q. Does that mean you prepare a

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number of dilutions?

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A. We prepare a number of dilutions which are then subjected to the next assay so that in case you don't make a proper dilution you don't have to do it a third time.

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Q. I see. Now, let us assume

just for the sake of illustration that there is a one to one dilution in the case of the sample which you dealt with. You dilute one to one and you reassay that diluted sample.

A. Yes.

Q. Do I understand that if at this stage you get a reading of 5 nanograms per millilitre, what is the concentration of digoxin in the sample?

A. The original sample?

Q. The one to one, yes.

A. Well, you multiply it by 2 and the concentration will be at least 5 to 10 nanograms per millilitre.

Q. If in fact you are still off the end of the scale on that dilution and it diluted four to one or three to one, or a combination of four - I don't know what the multiples would be, you would multiply whatever result came out in this case by four to get the concentration. Do I understand the principle correctly?

A. By the degree of dilution, yes.

Q. Mr. Cimbura, what is the lowest concentration this equipment can measure?

You say your scale is calibrated from .5 nanograms



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per millilitre. Is the equipment capable of measuring less than .5 nanograms?

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A. I believe it may be, yes, capable of measuring less than that.

6

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THE COMMISSIONER: Pardon me?

It may be capable or incapable?

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THE WITNESS: It may be capable, Mr. Commissioner. I am not really interested in concentrations below .5 but it may be. It's a very sensitive technique and in theory it may be capable of measuring even a lower concentration than that one.

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MR. LAMEK: Q. Is the .5 nanograms per millilitre on the RIA for digoxin what we could call the cut-off point for your measuring technique?

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A. Yes. After evaluation of the particular adaptation of the RIA, the experimental evaluation which was carried out in part by analyzing the samples of whole blood from children that were not on digoxin directly, I would be starting the cut-off, the experimental cut-off at .5 nanograms per millilitre.

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Q. Did you find on the analyses of blood of children who were not on digoxin therapy that you were recording apparently some digoxin in



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that blood?

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A. The recordings up to .5,
usually lower but up to .5. That is correct.

5

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Q. Does that suggest that below
that cut-off point of .5 an apparently positive
reading for digoxin may be a false positive?

7

A. Yes, because of the so-called
non-specific binding potential at the lower part of
the calibration scale and this is the danger when
one goes very low into digoxin through the RIA.

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Q. You may be recording substances
which are like digoxin that possibly react with the
antibodies which are not in fact digoxin. Is that
what you are saying?

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A. Well, actually I do not know
which substance specifically may produce this very
low degree of radioactivity so I am not sure if it
is similar to digoxin but it may be or it may not be.
I don't know which substance made this cross
radioactivity but this is characteristic - quite
generally known about RIA's in general, not only
for digoxin but for many other drugs.

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THE COMMISSIONER: I am a little
puzzled. You were in some doubt as to whether your
system or procedure would record readings under .5



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2 and then you are telling us about readings under .5.
3 It seems to me your system must record something
4 under .5?

5 THE WITNESS: You are right,
6 Mr. Commissioner. It records something but because
7 of our evaluation I regard anything below .5 as
negative.

8 THE COMMISSIONER: You are not
9 just that interested in anything under .5. The
10 machine will record it.

11 THE WITNESS: Yes, it will record
12 .5.

13 MR. LAMEK: Q. Do I understand
14 you and tell me if I have this correctly:
15 concentrations of less than .5 nanograms per
16 millilitre (a) you are not particularly interested
17 in such low concentration in any forensic context
18 and (b) you cannot be sure that at that low level
19 of measurement that it in fact is digoxin that is
being measured. Is that correct?

20 A. That is correct.

21 Q. And therefore as you have told
22 us you provide the .5 nanogram cut-off point.

23 A. That is correct and that is
24 based of course on our particular adaption of the

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procedure which we use and so on and they may vary
for other procedures.

4

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That is a topic I am going to
come back to in a moment, Mr. Cimbura, but you told
me a moment ago about a technique for separating a
sample of the real digoxin component as opposed to
that digoxin-like substance components. I think
you call that high pressure liquid chromatology?

9

A. Yes.

10

Q. HPLC?

11

A. That is correct.

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I am no more comfortable with
the initials than I am with the words. Can you
tell me, please, the principle upon which that
process operates?

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Yes, it will attempt to. The
equipment consists of a so-called column which is
packed or which contains a special absorbent material
which can vary depending on what type of HPLC one
wants to use. The drug after being injected or
introduced into the equipment under standard condi-
tions and controlled conditions is driven through
this column containing the special material by a
so-called mobile phase or a solvent of some sort
which helps to drive the molecules through the



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2 column that I mentioned before. Depending on the
3 partition co-efficient --

4 THE COMMISSIONER: I am sorry,
5 depending upon -- I didn't get the word.

6 THE WITNESS: Partition co-efficient.

7 MR. LAMEK: Q. Partition
8 co-efficient.

9 A. Yes, of a particular compound
10 which is determined by the solubility - I think is
11 the term which may be more familiar, which means
12 the mobile of the drug between the mobile face and
13 the packing in the column, the drug emerges from
14 the column at different times and the actual times
15 can be calculated by a comparison with the standard,
16 again standard amounts of digoxin and the time is
17 characteristic of a specific compound.

18 Q. Let me see if I understand that.
19 I don't pretend to understand the magic process but
20 in terms of its operation and how it works, do I
21 understand that when the sample goes into the
22 system and through the column you are able by
23 reference to a calibration that you have done with
24 the standard sample with a known content you are
25 able to say okay, what is coming off the column at
this point in time is not digoxin, it is one of



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2 those digoxin metabolites and what is coming off
3 at this point in time is another of those metabolites
4 and what is coming off in this point in time
5 sequentially is some other digoxin-like substance
6 which is not digoxin itself. It is only what comes
7 out between these two points in time that really
8 contains digoxin. Is that essentially what is
9 happening? You are extracting the digoxin from the
10 other components which you are not interested in
11 having. Having come off at different points in time
12 you are not interested in those. You do not collect
those. Is that a fair statement?

13

A. That is fair, yes, essentially.

14

Q. You are collecting the sample
as it comes out of the column, off the column within
the known period of time because you know from your
standards that you are in the period of time when
what comes off the column is digoxin and not a
digoxin-like substance. Is that correct?

19

A. That's correct, sir.

20

Q. How that magic is worked, I
do not begin to understand but that is the effect
of it, is it not? It is a separator technique,
if I can put it that way?

23

A. It is a separator technique.

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2 Q. Now, does the HPLC process as
3 it is used in your lab at the centre, does that
4 process measure the digoxin or do you use it merely
5 to separate the digoxin?

6 A. Well, as we used it at my
7 laboratory on analysis of digoxin from body samples -
8 we do not use the detector, the available detector
9 on the system. We again go into another RIA and
collect samples.

10 There is - I don't know whether I
11 was clear but there is some drugs there is a
12 detector on the equipment itself which is capable
13 of measuring some drugs and I suppose even digoxin
14 at very large concentrations and pure form; but the
15 technique as we have it set up for biological
16 material the detector which is present on the
17 equipment is not suitable for digoxin analysis and
18 for this reason we resort to use the RIA as so to
speak another means --

19 Q. So you take your separator or
20 refined sample off the high pressure liquid
21 chromatography, and having eliminated the digoxin-like
22 substance from those samples and you now put your
23 refined sample, the separator ^{ed} sample back through
the RIA?

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2 A. That is correct.

3

Q. Do I understand that the radio-
immunoassay of the refined sample that is now on
the HPLC, surely you would expect to provide you
with a more accurate and reliable reading of the
digoxin in the sample?

7

A. Yes, it could be.

8

Q. Because you believe you have
eliminated some of the cross reaction ^{ve} digoxin-like
substance by virtue of the HPLC?

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A. That is correct.

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MR. LAMEK: Mr. Commissioner, I am just about to move into something different. Is this an appropriate time for the morning break?

THE COMMISSIONER: Yes. I am so far removed from the practicalities of life, is 15 minutes enough or should it be 20 minutes?

MR. LAMEK: 15 will be fine.

THE COMMISSIONER: 15 is enough? I don't see any complaints. All right, we will take 15 minutes.

--- Short recess

--- On resuming:

THE COMMISSIONER: Yes, Mr. Lamek?

MR. LAMEK: Thank you, Mr. Commissioner.

Q. Mr. Cimbura, can we go back to what you told us was the purpose of the high pressure liquid chromatography which was to separate out the digoxin byproducts, the metabolites, the digoxinlike substances, so that what would be left for the RIA to measure is actual digoxin. Can we come back to that?

Are you aware of a report of some research work done in Vancouver in which blood samples were apparently taken from very young babies who had never received digoxin; a report done I think



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2 at the University of British Columbia, in Shaughnessy
3 Hospital by a group including a Dr. Seccombe. You
4 are aware of that?

5

A. Yes, I am, sir.

6

Q. And I should tell you that
7 Dr. Seccombe will be here to give evidence, and I
8 would prefer to ask you these questions after he
9 had been here; indeed you may want to come back and
10 give some other views and thoughts after you have
11 heard his evidence. But can I ask you this for now:
12 are you aware that when samples from those very young
13 infants who had not received digoxin were analyzed
14 for digoxin by the RIA method, readings were obtained
15 of up to 4 nanograms per millilitre of digoxin or a
digoxinlike substance? You are aware of those
findings, are you?

16

A. Yes. That is right. I think
if I recall it was referred to as a digoxinlike
substance.

19

Q. That is right. I think they
refer to it by the shorthand term DLIS meaning a
digoxinlike immuno^oreactive substance?

21

A. That is correct.

22

Q. Now you have already told us
that it is your understanding and you have never seen

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2 any literature to the contrary that digoxin is not
3 a substance that is manufactured by the body?

4 A. That is correct, sir.

5 Q. Is it fair to assume, Mr. Cimbura,
6 that if the B.C. children from whom those samples
7 were drawn had never received digoxin, whatever it
8 was that the RIA was measuring, it was not digoxin
9 itself? Is that a fair assumption?

10 A. Yes, I would think so. If they
11 in fact never received digoxin or perhaps their
12 mothers did not receive digoxin, yes.

13 Q. Is it also fair to assume,
14 Mr. Cimbura, that if the children had never received
15 digoxin or the qualifier you have added, if their
16 mothers had not had digoxin, that what was being
17 measured was not any metabolite of digoxin or any
18 degrade of digoxin or anything of that sort?

19 A. Yes. Any metabolite of digoxin
20 because you need to administer digoxin to produce
21 metabolite.

22 Q. That is right, but it seems from
23 the reports of the research --

24 A. If I may go back?

25 Q. Yes, of course.

A. I am not sure - you asked me if



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2 it is normal or reasonable to assume, I believe, that
3 it was not digoxin. On the basis of what I know
4 there is no digoxin produced in the body.

5

Q. Yes.

6

A. Of course the finding raises
a question that --

7

Q. And I recognize you can't say
anything more than either your experience or the
published literature enables you to say. I recognize
that.

11

A. Yes.

12

MR. STRATHY: I am sorry, I didn't
hear that last answer.

13

MR. LAMEK: Perhaps the Reporter could
help us.

15

THE COMMISSIONER: I have been warned
by the Reporters that it is very hard to read back.

17

MR. LAMEK: All right.

18

THE COMMISSIONER: Can we try it
without putting the pressure on the Reporter?

20

MR. LAMEK: Q. In fact it was not in
response to a question. You went back to an earlier
question I had asked you, was it fair to assume that
whatever was found was not digoxin?

23

A. Yes.

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Q. And I just can't recall for the
moment --

4

A. I qualified it to some extent
on the basis of what I know that to the effect that
digoxin is not produced in the body naturally I
would not normally think it is digoxin.

7

8

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Q. In other words --
A. But the finding raises questions.
Q. In other words, if I understand
you, Mr. Cimbura, you are saying it was assuming no
administration of digoxin to those children or perhaps
to their mothers, what was measured was not digoxin
unless, contrary to anything that has ever appeared
in any of the literature, digoxin is in fact produced
in the body?

15

A. That is correct.

16

17

Q. But you know of no literature
to support that hypothesis?

18

A. No.

19

20

21

Q. But apparently something was
reacting with the digoxin antibodies in that RIA if
the reports of the study are accurate, and of course
if the assay was properly performed with proper
materials.

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Let's make those assumptions. In that



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2 event the findings suggest that something was
3 reacting with the digoxin antibodies, do they not?

4 A. Yes.

5 Q. And presumably it would be
6 something, in light of what you told me this morning,
7 that had a chemical structure sufficiently similar
8 to that of digoxin to make it cross-reactive with
the digoxin antibody. Is that also fair?

9 A. Well, it could be something like
10 that.

11 Q. Yes. Well, it would have to be
12 something that was capable of binding with the anti-
13 body, wouldn't it, to be recorded on the RIA?

14 A. That is right, with the particular
15 antibody which was used, that is right.

16 Q. Now other than the known
17 substances which you have told us about this morning,
18 the metabolites of digoxin and the other two or three
19 drugs that you have mentioned, are you aware of any
20 endogenous substance, substance manufactured by the
body itself, that is cross-reactive with the digoxin
antibody?

21 A. No, not on the basis of published
22 information, literature, in humans, no.

23 Q. May we then go back to the HPLC,

24

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2 and can I put this hypothesis to you, Mr. Cimbura:
3 if indeed there is an unknown substance, an
4 unidentified substance, perhaps I should put it that
5 way, an unidentified substance, which in terms of
6 its chemical structure is sufficiently like digoxin
7 that it can and does cross-react with the digoxin
8 antibody, can you have any assurance that even what
9 you are taking off the HPLC column as digoxin may not
contain some of that unidentified substance?

10

A. Well, I believe I have what I
call reasonable assurance to a reasonable scientific
degree based on my knowledge of these techniques and
the fact that we were able to separate the substances
that we have tried and are known to cross-react from
digoxin. I have - I am reasonably satisfied that
what I am measuring on the HPLC is digoxin.

16

This belief is strengthened by some
more analyses which I had an occasion to perform in
the babies under this investigation, some babies
under this investigation, where I have used additional
modifications of the HPLC in one instance, and in
another instance I used the application of the
technique mass spectrometry, gas chromatography in one
instance, and they all confirmed my results, and the
identification of drugs in forensic toxicology is a

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2 matter of probability, and you may increase the
3 probability by various manipulations.

4 So I suppose to summarize my answer
5 would be I am reasonably satisfied that what I am
6 measuring after all our experimental work is digoxin.

7 Q. Is it not fair, though, Mr.
8 Cimbura, to say that your experimental work has been
9 directed to the separation of known digoxinlike
substances? Isn't that what HPLC is all about?

10 A. That is right. The potential
11 of the HPLC column, however, is not limited to the
12 substances which are known and which were tested. It
13 has a wide potential for separation.

14 Q. I appreciate that.

15 A. Another important part of our
16 evaluation was to study, to analyze blood from
infants that were not on digoxin therapy; that is,
17 blood after death. These infants died of apparently
18 other causes than digoxin poisoning, and the results
19 of these particular experiments do not confirm the
finding of the British Columbia group, in the sense
20 as I mentioned previously, that the highest
21 experimental value that was used there was about .5
22 nanograms per millilitre. And I should mention that
23 altogether we studied about 24, blood from 24 infants,

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and about half, as I recollect, were younger than
two months.

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Q. These were children who had not
received digoxin?

6

A. That is correct, yes. And of
course I am referring to our particular technique.

7

Q. Yes.

8

A. And our particular RIA antibodies
that we were using and so on.

10

Q. Fairly, Mr. Cimbura, and believe
me I don't mean to be anything but fair, you would
need to know I am sure a great deal more about the
technique and equipment and material used in the
Vancouver study; perhaps more about the age of the
children, a whole host of things, because you are
saying your experiments in that, your research in a
comparable area didn't duplicate the kind of results
that Vancouver's apparently produced?

18

A. That is correct, yes.

19

Q. It may not be fair - indeed it
would not be fair to ask you matters outside your
area of expertise, but you have said I think right
at the outset of your evidence that toxicologists not
only identify and measure concentrations of poisonous
substances in blood and tissue but they also are

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2 involved in the interpretation of results. Notwith-
3 standing that, if you are not comfortable with this
4 question, by all means tell me. But is it your
5 understanding, Mr. Cimbura, that a digoxin level in
6 the ante mortem blood of an adult within the range
7 of .8 to approximately 2 nanograms per millilitre is
generally thought to be within a therapeutic range?

8

A. That is correct.

9

Q. And consistent with therapeutic

10 levels of doses.

11

THE COMMISSIONER: Sorry. What was
12 that figure again?

13

MR. LAMEK: Q. .8 to 2 nanograms per
millilitre.

14

A. Approximately, yes.

15

Q. Is there similarly an approximate
16 recognized therapeutic range of digoxin in the blood
17 of infants, and if so, could you tell me what that
18 range is generally considered to be?

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THE COMMISSIONER: Infants I think

we should define. What do you think of as an infant?

THE WITNESS: Mr. Commissioner, I

think there can be different definitions.

THE COMMISSIONER: Well, the legal

one is 18, 19 if you want to drink but 18 for other purposes.

THE WITNESS: 18 months?

THE COMMISSIONER: No, 18 years.

THE WITNESS: 18 years. I personally

regard infants as up to about two years.

THE COMMISSIONER: All right.

THE WITNESS: But I'm not sure whether I'm an authority on that.

THE COMMISSIONER: All right.

MR. LAMEK: Q. Well, a child of, let us say up to two years, if that's your understanding, is there, to your knowledge, a generally accepted therapeutic range of digoxin concentrations in ante mortem blood?

MR. ORTVED: With respect, Mr.

Commissioner, I appreciate that Mr. Lamek has already qualified Mr. Cimbura's response by putting to him that he is an expert in this field, but it strikes me that we really are getting now pretty far afield



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from his expertise in toxicology. That is very much a question that should be put to a paediatrician or a pharmacologist, not a toxicologist, with respect.

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THE COMMISSIONER: Well, I don't know, but I would have thought that a person who is examining for toxic ranges would also know what therapeutic ranges were. Would he not have to know that, I don't know. This may just go to weight and it is certainly something that you can deal with in cross-examination. But surely he must know, must have some idea when he makes the test whether what he's finally producing is something that is normal or something that is abnormal, would he not?

MR. ORTVED: I suppose as long as

he makes it clear on what he is basing his information as to his generally accepted standard.

THE COMMISSIONER: Yes. Well, all

right. Well, we can certainly ask him that either before or after the answer.

MR. LAMEK: Perhaps he could answer

the question that's pending and then I will ask him the basis for the answer.

Q. Mr. Cimbura, is there, to your knowledge, an accepted, or generally accepted range of therapeutic concentrations of digoxin in the blood



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of infants which you have suggested are children of up to two years of age and, if so, what is that range?

A. Well, my belief in this regard is based primarily on reading and evaluating the many literature studies that have been done on the subject. The age has to be I think subdivided. Okay, if I may rephrase that. In younger infants - by younger I would refer to younger than six months or so - the therapeutic or normal range I would regard as somewhat higher than in the adults and generally has in the order of or up to about three or four nanograms per millilitre of serum or plasma.

Q. Mr. Cimbura then, may I ask you this. If, and I ask you ^{to} accept the condition for the moment, if the Vancouver reported results can be duplicated and if you were to record in the ante mortem blood of a child who had been receiving digoxin levels of 7 or 8 nanograms per millilitre, would you not have to consider whether that reading of 7 or 8 nanograms may still reflect a therapeutic range as you have defined it, taking into account the possibility that up to 4 nanograms may be of the unidentified substance reported from Vancouver?

A. Well ---

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Q. It was a very long and

involved question, forgive me.

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THE COMMISSIONER: I got a little lost

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too somewhere along the line.

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MR. LAMEK: Q. All right. Let me
spell it out to you in different conditions. Assume,
and this is basic assumption, that the Vancouver
results can be replicated ---

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THE COMMISSIONER: Let us have what

the Vancouver results are.

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MR. LAMEK: Of findings of up
to 4 nanograms per millilitre in the blood of children
who have never received digoxin.

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THE COMMISSIONER: Yes.

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MR. LAMEK: Q. Would it not follow
that a finding by RIA of up to 8 nanograms of
digoxin in the antè-mortem blood of a small child
up to six months of age may in fact be indicative of
a therapeutic range of the drug in that child, the
range which you have identified as perhaps 3 to 4,
because of the reading of 7 or 8, up to 4 nanograms
on the basis of Vancouver may not be digoxin at all.
Is that not something that you would have to consider.
I hope that's clearer.

THE COMMISSIONER: What you're asking



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H5 2 is, is 8 minus 4 equal 4?

3 MR. LAMEK: I may be asking that.
4 What I'm really asking is does 8 mean 8, or could
5 it mean as little as 4?

6 THE COMMISSIONER: Yes.

7 THE WITNESS: You didn't mention in
8 your question whether the results of 8 nanograms
would be by what technique?

9 MR. LAMEK: Q. I thought I said by
10 RIA?

11 A. By which RIA?

12 Q. By your RIA.

13 A. By my RIA?

14 Q. Because we don't know what
others do with it yet.

15 A. As I mentioned previously in
16 my RIA in my experience, my evaluation of my RIA
17 does not confirm the findings by the British
18 Columbia group.

19 Q. Yes.

20 A. I think it is a possibility
21 that it would enter one's mind and one would certainly
22 think about it. If I could have a result of 8 nanograms
23 per millilitre by our technology I would be concerned
about it and I think that child should be investigated

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2 by whatever investigation is needed to make sure
3 that he's receiving normal therapy. That would be
4 my first thought.

5 Q. Yes. And, indeed, that might
6 be the prudent thing to do in any event.

7 A. And I would probably also use
8 our confirmatory technique, or second technique to
do the analysis.

9 Q. Yes.

10 A. With 8 I would, yes.

11 Q. Well, I recognize the element
12 of unfairness that comes in putting to you bits of
13 that study and maybe we can move quickly to something
else, then, Mr. Cimbura.

14 So far we have focussed on digoxin
15 assays in ante mortem blood samples. Are the same
16 techniques that you have described there used on
17 post-mortem blood samples?

18 A. Well, the techniques that I
19 have described are particularly designed for post-
20 mortem samples and tissues, that's right.

21 Q. Well, let's leave tissues aside
22 for the moment. I am talking about blood for the
moment.

23 A. Primarily designed for post-mortem

24

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2 blood specimens.

3

4 Q. Do I understand then that
they be ante or post-mortem?

5

6 A. Yes, I would use the same
7 technique, even though ante-mortem specimens in a
8 hospital, I'm not sure whether that is what you are
referring to.

9

Q. No, I'm talking about your ---

10

A. The approach to the RIA may
vary, yes.

11

Q. Now, with respect to tissue
samples, tissues other than ~~from~~ blood or body fluids,
I assume that essentially we are talking about post-
mortem samples. I suppose you could have biopsy
samples, but for the most part we are talking of post-
mortem tissue samples, are we?

12

A. That's correct, sir.

13

Q. That are analysed. When the
Centre for Forensic Sciences became involved in doing
digoxin assays on children from the hospital in the
Spring of 1981, was there at that time, Mr. Cimbura,
a recognized technique or procedure for measuring
digoxin levels in tissue?

14

A. Well, there were some reports

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2 in the literature, relatively few as compared to the
3 ante-mortem blood specimens, and there was some
4 forensic literature that was available with respect
5 to cases of poisoning where the RIA procedure,
6 radioimmunoassay procedure was used, or were used,
7 and there were also relatively few research articles
8 in the literature with respect to utilization of the
9 HPLC more on the research conditions.

10 Q. And what technique was used
11 at the Centre for Forensic Sciences for the analysis
12 of tissue samples of digoxin?

13 A. It was similar to the technique
14 that I have attempted to describe for blood. There
15 were some modifications at the beginning in the sense
16 that of course tissue has to be broken down before
17 analyses has to be cut into small portions and
18 homogenized in a suitable medium and then the portion
19 of the homogenate is then subjected to the radio-
20 immunoassay procedure as I have described, including
21 the extraction process and so on.

22 Q. When you say homogenized, do
23 you mean essentially translated into a liquid form?

24 A. Into a semi-liquid form, a
25 homogenate, blending the matrix or the tissue with
26 some fluid, that's right.



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2 Q. And having put it into that
3 form, you then use the same RIA technique as you
4 have already described?

5 A. That's correct.

6 Q. But the results I think are
7 expressed differently are they not?

8 A. Yes. I have forgotten to
9 mention the first thing, the tissue, one has to
10 weigh the quantity which one deals and of course
11 the tissue being solid is measured in grams as
12 opposed to blood, which is a volume, it's measured
13 in litres.

14 Q. Yes.

15 A. So, results in tissues are
16 expressed as nanograms per gram of tissue, wet tissue.

17 THE COMMISSIONER: Mr. Cimbura, what's
18 the comparison in litres and grams. Would a gram
19 weigh, would a litre weigh a gram?

20 THE WITNESS: Well, millilitres.

21 THE COMMISSIONER: Millilitres, would
22 a millilitre weight ---

23 THE WITNESS: Millilitre would be close,
24 Mr. Commissioner.

25 THE COMMISSIONER: Depending upon the
26 substance.



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2 THE WITNESS: Yes, it depends on
3 the density of the substance.

4 THE COMMISSIONER: But it's not far
5 out.

6 THE WITNESS: It's not too far out.

7 MR. LAMEK: Q. One final question,
8 Mr. Cimbura, if I may. You have referred to
9 radioimmunoassay procedures and to high pressure
10 liquid chromatography. I understand that there is
11 a third technique that is now in use that involves
12 a fluorescent polarized immunoassay. Is that a
13 technique with which you have any experience?

14 A. No, sir. As I understand it,
15 that technique became commercially available very
16 recently and I am yet to receive the information on
17 it which is supposed to come to me.

18 THE COMMISSIONER: Can we just have
19 the name of this technique again?

20 MR. LAMEK: I believe it to be
21 fluorescent polarized - no, polarization, I'm sorry -
22 fluorescent polarization immunoassay.

23 THE COMMISSIONER: I hope we can use
24 initials for that too.

25 MR. LAMEK: FPIA, how's that. Now
I know why Mr. Cimbura prefers radio, it's easier



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1 to say than fluorescent polarization, whatever it is.

2

3 Mr. Cimbura, thank you very much.

4

5 Mr. Commissioner, before there is

6

any cross-examination of Mr. Cimbura, perhaps I
should make it clear again what I hope I made clear
yesterday, that Mr. Cimbura will be recalled to give
evidence as to the particular findings that he
recorded in the tissues that came to him from the
Hospital and perhaps any questions as to those
particular results might be reserved until that
evidence comes in at a later time.

11

12 THE COMMISSIONER: Yes, all right,

13

Mr. Lamek.

14

Now, on the cross-examination

15

generally, I suppose in the normal procedure I would
take counsel in the front row and second row and then
in the third row but of course you can agree to any
order you like and there may be instances where one
counsel would particularly like to be last and, if
so, he can apply for that privilege.

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Cimbura, dr.ex.
(Lamek)

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In this particular instance, I don't know. Perhaps everyone would prefer to start after lunch. I don't know what your thoughts would be. What about you, Mr. Bogart, you are first in line.

MR. BOGART: Yes, Mr. Commissioner. I would prefer to start afterwards.

THE COMMISSIONER: Then perhaps you can confer if you want and if you don't I will just call on counsel in the order in which they should be.

All right. Then would 1:45 suit everyone? That would be an hour and a half. All right, until 1:45.

MR. LAMEK: Mr. Commissioner, before you rise perhaps I could ask this because obviously there is a schedule question here to be mulled over during the lunch hour. I do not know whether counsel are in a position to let me know whether they propose to cross-examine. If I could even have the ~~fairlest~~ fairest idea it would be helpful for me.

THE COMMISSIONER: Yes, we will perhaps know a lot better from their performance afterwards, but perhaps you could tell us now if anyone is disinclined at this moment to cross-examine. Does anyone wish not to cross-examine at all or has at least made up his mind he will not. You will not



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2 be held to this of course.

3 I think you can count on the entire
4 group.

5 All right. Until 1:45.

6 ---Luncheon recess at 12:10 p.m.

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JC/ak
2 ---Upon resuming at 1:45 p.m.

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MS. CRONK: Mr. Commissioner,

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Mr. Lamek is undoubtedly on his way into the Court
5 Room. With your indulgence I will look for him.

6

THE COMMISSIONER: Will you do that,
7 thank you.

8

Have you given any thought to the
problem of the order of cross-examination? If not
I am just going to take everybody in order. Perhaps
it is unnecessary to have Mr. Lamek here.

11

MR. BOGART: Yes, Mr. Commissioner.

12

My understanding was that Mr. Scott was prepared
to cross-examine first. However I see he is not
13 here.

14

MR. WELLS: Mr. Commissioner, I am
15 Ross Wells from Mr. Scott's office. He is on his
16 way. I am not sure that he understood he was to
17 go on first.

18

THE COMMISSIONER: You can fight
that one out.

19

MR. WELLS: He will be here
20 momentarily. I am sorry for the delay.

21

THE COMMISSIONER: Anyone else
22 want to have this honour?

23

What about you, Mr. Ortved?

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2 MR. ORTVED: Yes, Mr. Commissioner.

3

CROSS-EXAMINATION BY MR. ORTVED:

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Mr. Cimbura, what we have really been talking about today is the measurement of the amounts of digoxin in bodily fluids or tissues. Is that correct?

5

6 A. That is correct, sir.

7

8 Q. You told us about the various
9 methods available and to some extent utilized by
10 you to ascertain those measurements. Is that
11 correct?

12

A. That is correct.

13

Q. And the toxicology, you have told us, is a science of first ascertaining the measurement and secondly interpreting those measurements. Is that correct?

14

15

A. That is correct, sir, if possible.

16

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Q. And really the thrust of your testimony has been the degree of accuracy to which you can qualify your results. Is that correct?

18

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A. Well, we were talking about the methodology of the use for digoxin analysis.

20

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Q. Right. If I understood your evidence correctly, you were indicating some methods

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may give more accurate results in terms of actual
digoxin in the sample than others.

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Essentially that is correct,
yes. As I mentioned previously the analytical
methods in general that are used in forensic
toxicology each has some advantages and some
disadvantages and it's a matter of experience and
where it goes out.

5

Q. Just to summarize: as I
understand you told us that one of the problems
with the RIA method is that you may to some extent
be measuring quantities of digoxin-like substances
as opposed to digoxin.

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A. That is one of the disadvantages
of RIA.

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Q. It is by the same token one of
the advantages of the HPLC method in that it,
according to your evidence, hopefully screens out
the digoxin-like substances?

A. That is correct, sir. Pardon
me. I'm coming with some throat irritation. My

voice may be --

Q. Would you like some water?

A. Yes, I would appreciate that,
thank you.



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Q. But I take it you would agree with me that the result you made on your test, be it the HPLC or the RIA, may be inaccurate in terms of the actual level of digoxin in a body as opposed to a sample having regard to a whole hosts of factors?

Correct?

A. I'm sorry, I don't understand the question.

Q. Well, as I understand you told us toxicology is not just a measurement of results but also an interpretation of the results. You told us also that you could measure certain samples and you have given us your evidence as to how accurate the result in terms of your findings as to digoxin is in terms of that sample. Right?

A. Yes, okay.

Q. I am simply suggesting to you as to whether or not the reading of the digoxin level in that sample is an accurate reflection of the digoxin in, for instance, a child's body and is not always one and the same.

A. I am not sure if I still correctly understand the question but I will try to explain it. Please correct me if it's not the answer you expected.



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Q. I will.

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A. The analysis in post mortem specimens, let us say, of a blood sample result may not be the same as the value in the same specimen before, let us say, a child died. Is that what you are saying?

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Q. Right. That is one of them and that is I take it something about which there is no dispute. Correct?

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A. Well, there has been - yes,

generally there is - this is recognized. That is a factor.

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Q. And in fact if I understand the situation, post-mortem values which you may get on analysis of samples taken post mortem may differ from actual pre-mortem levels by a factor of 3 or even 4. Correct?

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A. I don't understand just the question.

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THE COMMISSIONER: You are assuming that no digoxin has been ingested by the deceased between the last calculation ante mortem and the calculation post mortem.

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MR. ORTVED: Right.

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THE COMMISSIONER: Do you understand



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2 that, Mr. Cimbura? Assuming that no digoxin went
3 into the body from the time that the sample was
4 taken ante mortem and the taking of the sample
5 post mortem, is there a difference and if so what?

6 THE WITNESS: Yes, there can be
7 a difference and I would just like to make sure we
8 are talking about the same situation. I am referring
now to a sample of blood --

9

MR. ORTVED: Q. All right.

10

A. Taken after death from a person and comparing that sample of blood to an ante mortem sample assuming, as was mentioned, that no dose was given in between or else to the sample at the time of death, near about at the time of death and according to work that has been done on human studies and the literature there can be differences and the degree of differences, for instance, would depend to a considerable degree where the post mortem blood was taken from but there would tend to be differences and I would agree that post mortem values may be higher than the values on the ante mortem to some degree.

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Q. Let me just confine my questions for the moment to the question of blood and I will talk about in different sites for the moment, but I am

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suggesting to you if you were to take a sample of blood from, for example, the sagittal sinus area pre-mortem and then take a sample of the sagittal sinus blood some period of time post mortem, assuming that there has been no administration of digoxin in the interim, I am suggesting to you and you have told me that you would anticipate that the level of post mortem would be higher than pre-mortem?

A. It could be higher. I would

like to mention - you are using as your example blood taken from the sinus you would have to ask a pathologist or a physician whether it is possible it could be taken post mortem from that source.

There could be an elevation in the post mortem blood but sagittal sinus I regard as one source of blood at least in my experience where the degree of elevation after death is smaller than in some other sources of blood.

Q. That is right. That is why I

picked it. But I am suggesting too that the literature speaks/the possibilities that ante mortem blood can give a reading - excuse me, post mortem samples of blood can give readings ^{as much} such as three or even four times higher than pre-mortem blood.



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A. Yes. With reference to blood
taken from the heart. That is my opinion based on
work that has been done in the literature, that is
right.

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THE COMMISSIONER: Blood from the
heart can give a reading of three or four times
what the ante mortem reading would be.

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THE WITNESS: That is right. Up
to, Mr. Commissioner, up to. That is the upper
limit. That is being determined in all the studies
that had been done.

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MR. ORTVED: Q. So just to bring
this back to where we were this morning.

A. If I may - sorry, if I may
qualify, sir. This may happen. It doesn't
necessarily happen.

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THE COMMISSIONER: May happen.

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THE WITNESS: It may happen. It
doesn't necessarily happen. That is right. The
elevation may be less than that.

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THE COMMISSIONER: You said blood
from the heard. Did you want to emphasize "from the
heart", that it might not be blood from some other
section?

THE WITNESS: I am not sure whether



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I have enough information to be able to distinguish those two in this regard but yes, I would expect that the elevation may be up to three to four times in the blood taken from the heart but it could be smaller than that.

THE COMMISSIONER: I was wondering.

You said from the heart. You seem to indicate it came from the heart, if I can put it that way. It wasn't part of the question. I am just wondering why you said from the heart? Is there some distinction between the heart and the brain?



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/EMT/ak

THE WITNESS: Well, one reason is that in forensic work, in the work that has been reported in the literature, blood taken from the heart has been studied and described more than any other source of blood so that there is virtually more information on blood taken from the heart.

From theoretical considerations it seems logical because the heart tissue does have considerable normal concentrations of digoxin much higher than blood, so that - and the theory is that after death when the membranes and the cells are becoming - are dying or are dead, that there is a diffusion from an area of high concentration to an area of low concentration.

THE COMMISSIONER: You are talking about blood from the heart? You are not talking about the heart itself, tissue of the heart?

THE WITNESS: I believe we are talking about blood from the heart, that is right.

THE COMMISSIONER: Sorry, Mr. Ortved.

MR. ORTVED: Thank you,

Mr. Commissioner.

Q. So, Mr. Cimbura, coming back to the levels that were spoken of this morning, we were using I think a level of 4 as being maybe the

RE-EXAMⁿ re these studies. When? Purpose?

34 infants.

On digoxin therapy prior to death.

Have anti-muscarin blood levels?

Some of same p.m. samples studied?

Heart blood?

RIA or HPLC + RIA?

Highest p.m. level 12.4 ng/ml.

Know what a.m. level had been

Lowest p.m. level.

Avg p.m. level. in ng/ml

— as multiplier of a.m. level?

St. child w. highest p.m. level (12.4 ng/ml)

had received last dose of digoxin

2½ hrs before death.

Significance of info

[NB: Tycho, p. 173, l. 16).

Other aspect
re importance
of knowing
time of death.

1.173, L. 17213.



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upper end of the therapeutic range for a very small infant. What I am suggesting to you is if you in your analysis of a sample of blood from a heart taken post mortem were to come up with a value of 16, then on the basis of what you have told us I take it that you would have to consider that that may have indicated a value within the therapeutic range ante mortem? Correct?

A. On that basis, yes.

In addition to what I have said, however, I have conducted studies at the Centre where we studied the extent of the elevation, or the extent of the blood levels after death of children who were on digoxin therapy and who died of natural, apparently natural causes other than digoxin overdose, and in my work we have studied specimens of blood taken from 34 different children on digoxin therapy, and the highest value I have seen in the post mortem blood from the heart was 12.4 nanograms per millilitre. This again I would like to emphasize is only one of these 34 infants that I have studied.

Going back to similar data that has been published in the literature on the post mortem levels of digoxin in the blood, the highest value that I have seen in all the literature published was



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a value of 15 nanograms per millilitre.

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Q. All right. I don't think you
and I are frankly that far apart because I think
my simple point to you is that the one child which
you got a value of 12.5 from heart blood post mortem
is not necessarily to say that that child was not
in the therapeutic range pre-mortem.

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A. Well, I would regard - this is
what I found - I would regard that as the extreme --

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Q. Right.

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A. -- upper limit. As a matter
of fact going into details about a particular child,
I have knowledge that the child received his last
dose only two and a half hours prior to death which
could mean that the blood - that the digoxin was not
yet at the so-called ~~study~~ ^{slightly} stage. It was higher
than it should have been normally. So there was
some explanation for this extreme high value that
I found.

Q. And I'm going to come to that
part actually too in my questions, but just to take
up where you left off there, in fact what you are
telling us is that digoxin when first administered
peaks fairly quickly and then comes down in terms of
its level in the blood until it reaches its level



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of equilibrium some perhaps six hours later, and
you are telling me that because the samples taken
in that six hour period (namely after two and a
half hours) it may have given unrealistic readings.

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Is that correct?

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A. High reading, that is right.

5

Q. Right.

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A. I am not - you know, you
described some of the peak effect and so on. I am
not sure whether those were your comments, whether
you wish me to comment on them.

7

Q. I will come to that. But going
back to the business of factors that may affect the
ante mortem reading as opposed to a post mortem
reading you have told us now about a factor of
3 or 4 that may raise the post mortem reading
over an ante mortem reading.

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It also depends, as you have already
intimated, from where the blood comes. Correct?

9

A. The elevation by a factor of
3 to 4 pertains to blood taken from the heart.

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Q. Correct.

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A. That is right.

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Q. And as to the sample you have
and the indication from that sample relating it back

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to the level in the body, different parts of the
body give different readings, do they not?

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A. I am sorry; I am not clear on
that.

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Q. All right. If you take blood
from the heart you have already told us you expect
to get a higher reading than blood taken from the
sagittal sinus area.

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A. That is correct. I expect to
get higher possible elevation.

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Q. Possible elevation.

A. Over ante mortem blood.

Q. Over ante mortem blood. So

the factors we have to consider are firstly in terms
of relating back to the child's level pre-mortem.
We have to consider, number one, is this a post
mortem sample, and if so, there may be a factor
of 3 or 4 possibly.

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A. If it is from the heart.

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Q. If it is from the heart. And
secondly where does the sample come from? Correct?

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A. The sample of blood you mean?

22

Q. Yes.

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A. Well, yes. If I may expand on
it a little bit, the extent of what is known regarding

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the post mortem blood, as I have mentioned before
most extensively studied was blood from the heart.

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There are reports in which is mention
that blood, post mortem blood, taken, for example,
from peripheral veins after death, such as femoral
vein, the elevation would be expected to be at less
than for heart blood.

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And from my own experience I have
found that in case of blood taken from sagittal
sinus from infants --

THE COMMISSIONER: The sagittal is part
of
/the brain, is it?

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THE WITNESS: It is - in the
similarities, taken from - yes, that is right,
Mr. Commissioner.

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From my own experience I have found
that blood from sagittal sinus gives the lower
reading, if you want to call it, than blood from the
heart, than corresponding blood taken from the heart.
Those are the three main sites of blood, post mortem
blood, that have been either studied by myself or
referred to in the literature.

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MR. ORTVED: Q. All right. So
when you talk about your generally accepted therapeutic
range for infants, to what site are you making



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reference in terms of results given by the sample?

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A. Are you talking about post
mortem therapeutic range?

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Q. No, if we are talking about
therapeutic range I take it we are talking about
pre-mortem.

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You indicated in your evidence this
morning you accepted that a fair therapeutic level
for an infant would be something up to 4 nanograms
per millilitre. Is that correct?

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A. As a general guideline, yes,
up to about 3 to 4 in a pre-mortem sample of plasma
or serum, that is right.

14

Q. Yes.

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A. And this is my guideline. There
may be instances where some higher levels may be
seen by clinicians, you know, that may not cause
toxicity, but this is my sort of a guideline, yes,
that is right.

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Q. And you told us that in the
same child a sample taken from the heart would vary
in your experience from a sample taken from the
sagittal sinus?

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A. Yes. That is a variation due
to post mortem. I didn't refer to the variation in



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source of blood before death.

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Q. All right.

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A. I was referring to post mortem sources.

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Q. That is just what I want to make clear. And in an infant pre-mortem would you expect that the level would be uniform in the blood throughout the body?

9

A. Well, as I have mentioned before I have not seen any studies that have compared, have compared different sources of blood before death.

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Q. All right.

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A. With respect to different concentrations that may be involved. But if the blood is taken from the usual peripheral circulation, I generally would not be concerned about the source of blood if it is taken from an intact vein or artery before death.

19

Q. All right.

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THE COMMISSIONER: The figures you gave us for the therapeutic level this morning I take it were ante mortem figures, were they?

THE WITNESS: Those were ante mortem, that is correct.



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THE COMMISSIONER: .8 to 2 nanograms
in adults and for infants at least under six months,
it is
higher than adults and it is up to 3 or 4? 3 or 4
nanograms. Those figures are ante mortem figures,
are they?

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THE WITNESS: That is correct.

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Ante mortem.

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MR. ORTVED: Q. Okay. So just
to review, if you are examining samples post mortem,
that have been taken post mortem, samples of blood
and you wished to get the closest approximation in
your expertise of the level pre-mortem, then you
are telling me that, number one, you would like to
have a sample from the sagittal sinus?

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2 Q. That's right. And the reason
3 that the sample from the heart is unsatisfactory as
4 far as you are concerned is because, in your ex-
5 perience, it can somehow multiply by three or four
6 times following death?

7 A. It may multiply.

8 Q. It may.

9 A. Up to that.

10 Q. All right.

11 Then another matter that came out
12 in the questioning on the part of Mr. Lamek --

13 THE COMMISSIONER: I'm sorry, I
14 didn't understand him to say that there was that
15 distinction between the heart blood or the brain
16 or the vein blood.

17 Your question was -- I would like to
18 get it cleared up, if I may.

19 Your experience is almost entirely,
20 is it not, post mortem in the heart?

21 THE WITNESS: Yes, post mortem blood
22 from the heart and sagittal sinus.

23 THE COMMISSIONER: Yes. Now, I know
24 you have said that the tendency is for the heart
25 blood to be of a higher reading than the brain; is
that right?



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2 THE WITNESS: Than the blood from
3 the sagittal sinus.

4 THE COMMISSIONER: Right. The
5 question Mr. Ortved put to you was --

6 MR. MANNING: Mr. Commisssioner, we
7 can't hear you back here.

8 THE COMMISSIONER: Well, it certainly
9 is my fault because I have been found not to be
10 able to operate this machine. Is it on now? Yes?
All right.

11 Just to make it clear for me, will
12 you just tell us, if you can, what the differences
13 are, if any, between, on the one hand, ante mortem
14 blood and, on the other hand, post mortem blood
15 taken from the heart blood or the brain or the leg
veins? Were those the three areas you mentioned?

16 THE WITNESS: Yes.

17 THE COMMISSIONER: Can you do that?
18 Can you tell us what differences you expect and,
if so, can you also tell us why.

19 Did you get any of that, Mr. Manning?

20 MR. MANNING: Yes.

21 THE COMMISSIONER: That may not be a
22 question but you can refine it after he has given
23 the answer.

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2 THE WITNESS: Yes. I will attempt
3 to do that, sir.

4 THE COMMISSIONER: Assuming in every
5 case that there has been no intervening dosage of
6 digoxin.

7 THE WITNESS: That's right.

8 When one compares the post mortem
9 blood; that is, blood taken after an autopsy, from
10 the heart and the digoxin concentration in this
11 blood could be elevated up to a factor of three to
12 four times over the value present in the blood taken
13 immediately before that.

14 THE COMMISSIONER: Yes. All right.
15 Do you have this information?

16 THE WITNESS: I beg your pardon?
17 THE COMMISSIONER: What would it
18 likely be if the blood came from the brain or it
19 came from the leg vein?

20 THE WITNESS: I'm not sure I can
21 draw the factors here, other than saying I would
22 expect it to be less.

23 THE COMMISSIONER: All right.
24 Now, can you tell us why, if you can,
25 first of all, it would be three to four times greater
from the heart and why it would be less if it comes



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2 from the brain or the veins?

3 THE WITNESS: With respect to the
4 post mortem blood taken from the sagittal sinus,
5 I have done a comparison on, as I recall it, blood
6 taken from fourteen children where both the blood
7 from the heart was available and the blood from the
8 sagittal sinus was available. On the average, the
9 digoxin concentration in the blood from the saggital
10 sinus was about 59 per cent of the digoxin concentra-
11 tion in the blood from the heart.

12 This personal research is one of the
13 reasons which allows me to expect a lower degree of
14 elevation after death in the blood taken from the
15 sagittal sinus.

16 THE COMMISSIONER: Can help us as
17 to why, or not?

18 THE WITNESS: Well, I'm not sure
19 whether anybody can be definite as to why.

20 I think one of the reasons, I suspect,
21 is involved is that, getting back to the heart, the
22 normal concentrations of digoxin in the heart are
23 much higher than the normal concentrations of digoxin
24 in the blood.

25 THE COMMISSIONER: Well, the problem
about that is that, presumably, you were comparing



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2 the digoxin levels in the heart post mortem and the
3 heart pre-mortem. You can't very well take blood
4 from the heart on pre-mortem, can you, or ante
5 mortem?

6 THE WITNESS: No. What I was com-
7 paring in my experiments, if I may correct myself,
8 is tissue of heart taken after death, with the blood
9 of the heart taken after death, and one explanation
10 for the relatively high elevation in the blood from
11 the heart is the diffusion after death of the digoxin
12 with the weakening of the membranes that hold the
13 drug while the person is alive. After they are
14 dead, there is a weakening and dying of these
15 membranes and there is a diffusion from the relative-
16 ly high concentrations in heart tissue into the
17 blood surrounding that tissue.

18 With respect to brain, for example,
19 on the whole, I would expect that brain concentrations
20 would be relatively much lower than heart concentra-
21 tions. The same reason could be applied to blood
22 taken from peripheral veins, such as the femoral
23 vein, where the concentration in the muscle, in the
skeletal muscle which surrounds these veins, again,
is not as high as the normal concentration in the
heart.

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25



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2 So, that could be the explanation
3 that has been looked at by various investigators.

4 MR. ORTVED: Q. All right. Have
5 we dealt with the business of the femoral vein, Mr.
6 Commissioner?

7 MR. SCOTT: Well, just before my
8 friend, Mr. Ortved, goes any further, I look to
9 Mr. Lamek at a certain stage to give us direction
10 because I presume that we are not going to have to
11 cross-examine every witness throughout this enquiry
12 if he is asked questions and responds beyond the
13 area of his expertise.

14 I just want to get from Mr. Lamek
15 a direction about that in due course so that I won't
16 feel obliged to pursue every area just because a
17 question has been asked about it.

18 THE COMMISSIONER: Yes. I think I
19 can only agree. Are you asking me to agree with
20 what you are saying or to excuse you from cross-
21 examination, or what would you like?

22 MR. SCOTT: Well, Mr. Commissioner, it
23 is a problem.

24 THE COMMISSIONER: Yes, I know.

25 MR. SCOTT: There is the Science of
26 Pharmacology and there is the Science of Medicine,



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2 for example. I am sure Mr. Cimbura will agree that
3 the question of what is a therapeutic dose is a
4 question for doctors. He and I have this in common -
5 we are not doctors. He certainly could have read
6 somewhere what a therapeutic dose is, but I am sure
7 he wouldn't want to, because he has been asked a
8 question about what he's read, give evidence as a
9 doctor about what is a therapeutic dose. And the
10 same thing has occurred with a whole range of
questions about the movement of digoxin in the body.

11

He's a chemist, as I understand it,
12 and an excellent one, and a tester, and an excellent
13 one, but that kind of question is for a pharma-
14 cologist, and I just don't want to be obliged to
examine because the evidence has been given.

15

THE COMMISSIONER: Well, Mr. Ortved,
16 I am not absolutely sure that Mr. Scott wasn't
17 really addressing you instead of me.

18

MR. ORTVED: I think that might have
been the case. I think I appreciate his assistance.
19 I am merely concerned with the aspect of Mr. Cimbura's
20 testimony this morning to the effect that, if he got
21 a result of one of his analyses before death --

22

THE COMMISSIONER: But, surely, that's
23 legitimate evidence that he did get results. If he

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2 does get those results, it may not be so legitimate
3 or, at least, it may not be asking to give much
4 weight as to his reasons why; that's all. But the
5 fact that his experience has shown these dif-
6 ferences, I should think is valuable evidence.

6

7 MR. ORTVED: All right. I am not
8 going to be that much longer in any event, Mr.
Commissioner.

9

10 Q. The two other aspects I want
11 to canvass I think you have already touched upon,
12 and that is, firstly, that, in terms of relating
13 your findings back to a child pre-mortem, you have
14 already told us you have to have regard for the
timing of the administration of the digoxin; correct?

14

15 A. Well, certainly, the timing
16 of administration of digoxin would be relevant to
17 the extent of the blood level pre-mortem, which
could then affect the possible elevation after death.

18

Q. Right.

19

A. That's right.

20

21 Q. And, again, I don't want to
necessarily repeat myself but, as you are aware,
22 there are various means by which therapeutic doses
23 of digoxin can be administered; correct? By way of
injection, by way of intravenous, by way of oral

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25



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2 administration?

3

A. Certainly, yes.

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Q. Certainly. And each of those
5 varying methods of administration have different
times for distribution?

6

A. Well, I would like to qualify
7 that, if I may, rather than just answer yes or no.

8

May I?

9

Q. Yes, by all means.

10

A. Essentially, after a parenteral
11 administration of intravenous administration,
initially, as one would expect, there is a relative-
12 ly large quantity of digoxin in the blood within a
13 very short time after the administration. Subsequent
14 to that, it decreases rapidly.

15

Q. Right.

16

A. Which signifies the process of
distribution.

17

Q. Right.

18

A. So that, by about four to six
hours, it should be at the so-called steady state,
which is the time these normal levels that we were
referring to apply.

19

Q. Right.

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A. After an oral administration,

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2 the situation is somewhat different. Of course,
3 the drug is absorbed from the stomach and the gastro-
4 intestinal tract, so that, initially, there is a
5 rise of the concentration in the blood up to a peak
6 which may occur at about two to three hours and,
7 by four to six hours, the blood concentration again
8 is down at the steady state at which the normal
levels which I have mentioned apply.

9 It is a normal pharmacological
10 consideration for any drug.

11 Q. Right. And just so that Mr.
12 Scott won't be upset, that is something, I take it,
13 you would agree would be best explained by a
pharmacologist; correct?

14 A. Well, I would have to -- it
15 could be explained by a pharmacologist. I have
16 studied pharmacology; it was part of my studies.

17 Q. But in any event, the point
18 arising out of what you have just told us is that it
19 is important for you, as a toxicologist, in terms of
the interpretation of your results, to know, if
possible, the timing of the administration of the dose?

21 A. Yes, it is important for me,
22 as a toxicologist, to understand the principles that
23 are involved in these studies, yes.

24

25



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Q. Right. Because what you are telling me is that the timing affects the level?

4

A. That's right.

5

6

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9

Q. And, in fact, what may appear to be a high and, therefore, non-therapeutic level, if, in fact, it was taken within thirty minutes after an intravenous administration of digoxin, may not give the true level of the drug at the steady state?

10

A. That's correct.

11

MR. ORTVED: Thank you. Those are my questions.

12

THE COMMISSIONER: Fine.

13

Mr. Scott, are you next?

14

MR. SCOTT: I'm ready.

15

CROSS-EXAMINATION BY MR. SCOTT:

16

Q. Mr. Cimbura, when did you begin your professional career? Did you say it was in '59?

17

18

A. In '59 I graduated from the university and, in '61, I started with the Centre for Forensic Sciences, that is correct, sir.

19

20

Q. And did you begin in the Toxicology Centre?

21

22

A. That's correct, sir.

23

24

25



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2

Q. And have you been there ever
since?

4

A. That's correct, sir.

5

Q. Is your life as boring as
mine?!

6

A. I should modify it. I have
been, since last year, a Deputy Director of the
Centre.

9

Q. I see.

10

A. So, I am not there for most of
the time.

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JC.jc
DD

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Q. I take it that since that time when you began in the Toxicology School you would have done hundreds of thousands of tests on blood, whole blood, serum, plasma or tissue for toxicological purposes?

3

A. I am not sure, I don't think it was hundreds of thousands. I have done a lot.

4

Q. And did I understand you to say that until the problem at the Hospital for Sick Children you had never been required to do a test for digoxin in the Toxicology Centre?

5

A. Up to the time we had no facilities available for the analyses and the analyses was arranged by courtesy of other agencies.

6

Q. I see. Your Centre up until that time had never done a test on any of those substances for digoxin?

7

A. A test by using the same techniques as I have described.

8

Q. Yes. Had you ever done any digoxin tests before the Hospital for Sick Children incidents at your Centre?

9

A. I may have been - I cannot recall but a long time ago when I began there may have been occasions of suspected digoxin poisoning.

10

11

RE-EXAM^N: Re no prior experience (esp' w/
RIA) re dig. analyses pre-March/81:
Have to start from scratch to develop a
procedure?
— Prior experience w/ RIA for other substances
— Have RIA equipment at cost?
— Literature available in learned journals
re digoxin analyses by RIA.
What did you do when had to embark
on dig. analyses.
Seek any assistance ^{from the}
— any hospital.



DD.2

1

2 Q. But you cannot remember?

3 A. I can't recall whether I was or
4 not involved with them but the techniques were
5 certainly different then.

6 Q. So just so I am clear. If you
7 did any years ago it would have been on the basis of
a different technique?

8 A. That is right.

9 Q. But you can't remember in fact -
10 I do not criticize you for this - whether you ever did
11 any at all?

12 A. That is right.

13 Q. In any event until the Sick
14 Children incidents you didn't have any equipment for
15 performing the tests on a modern basis at the
Toxicology Centre?

16 A. We had the equipment. We didn't
have set up any evaluating procedure for digoxin.

17 Q. So this exercise which began in
the spring of 1981 was a new life experience for you
people, as well?

18 A. Oh yes.

19 Q. I just want to ask you something
about what you have read to see if it conforms with
20 what I have read. I know Mr. Ortved will forgive me

21

22

23

24

25

RE-EXAM: Re distribution of digoxin in body
(if so, basis for it).
Have any understanding for pattern of
dist^b — Scott said finds it may be
heart, muscle, shoulder muscle, big toe.

Sep. 195.
15.

Equal distribution throughout organs and
tissues?

Understanding as to areas, organs, tissues
of higher concentration?



DD.3

1

2 if I just - having made an objection, get into this
3 area but what we have read about digoxin: isn't it
4 true that you have read that digoxin can be taken a
5 number of ways, by injection, by mouth, theoretically
6 even intramuscular injection as well as intravenously?

A. Yes, that is correct.

7

Q. And that if we look at the case
8 of intravenous injection for a minute, it is injected
9 into the bloodstream under some kind of pressure
10 usually?

11

A. It is injected.

12

*

13

Q. Right. When it enters the
bloodstream over a period of time it works its way out
of the bloodstream into the tissues of the body.

14

*

15

A. Yes, generally speaking, yes. It
begins to -- .

16

*

17

Q. And then it will find its way
to a great variety of tissues in the body from the
heart muscle to the shoulder muscle to the big toe?

18

*

19

A. That is right.

20

*

21

Q. And then once it is in the
tissues of the body it then begins to break down and
filters its way out through the renal system or
perhaps the stomach?

22

*

23

A. Yes. It is relatively -- the

24

25



DD.4

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2 breakdown as I mentioned previously is relatively
3 minor. It is secreted mainly through the renal
4 system.

5 Q. And other things we know from
6 the readings are that the concentration of digoxin
7 will vary from or may vary from tissue to tissue?

8 A. You are referring to after death?

9 Q. I am referring to any time; once
10 that digoxin gets from the bloodstream into the tissues
11 then what we know from the readings is that there may
12 be more of what - what are they called - glands -
there may be more sites in some tissues than others?

13 A. That is right.

14 Q. And therefore the concentration
of it ante mortem may vary from tissue to tissue?

15 A. That is right.

16 Q. So what we know from those
readings very simply is that you may very well get
17 different readings depending on the tissue that you
18 take your test from or where you took it from the
19 blood?

20 A. From different tissues you can
give different readings.

21 Q. Yes. So one of the first things
you want to know is whether it was a blood sample,

22

23

24

25



DD.5

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2 whether it was a tissue sample and where it was taken?

3 A. Whether it was a tissue sample.

4 Q. Or if it was a blood sample. You
5 want to know where it was taken; right?

6 A. Well, I want to know where it
7 was taken. If it was taken from even from a peripheral
vein I wouldn't be concerned with it any more.

8 Q. So is it not true to say that
9 whether it is tissue or blood one of the things you
10 want to know is where the substance that you are
11 testing came from in the body of the person?

12 A. Where the sample came from?

13 Q. Yes, right. "

14 A. Well, I would want to know
15 whether it was blood or tissue.

16 Q. Let me put this example to you.
17 If I inject digoxin into my bicep, my left bicep, and
18 fifteen seconds later you take a blood sample from
19 my left bicep you are going to get a very different
reading than if fifteen seconds later you take a
20 blood sample from my right bicep, aren't you? Isn't
21 that right?

22 MR. MARSHALL: You will have to ask a
pharmacologist.

23 MR. SCOTT: Q. I am just asking if I

24

25



DD.6

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2 understand the readings. Am I right about that, from
3 your understanding of the readings?

4 A. I haven't done the particular
5 experiment you suggest.

6 Q. Will you go this far with me
7 that what you know from the readings, certainly with
8 respect to tissue is that you want to know where in
the body this sample came from?

9 A. That is right.

10 Q. With respect to blood you are
11 going to wait a little while before you answer that
question because you have never done that test?

12 A. I have done some tests in ante
mortem samples, not as many as in post mortem samples.

13 Q. The second thing you will want
14 to know before you take your sample is how long
15 before the digoxin was injected into the system, would
16 you not?

17 A. Well you want to know for
18 certain information, for example, you don't require to
19 know it for the analysis but you require depending on
20 what you want to know, that is right.

21 Q. Well now, you are here to tell
22 us about your testing. I want to ask you a couple of
23 questions about it just to be sure I understand what

24

25



DD.7

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2 you did. Now, do I understand you can do a test on
3 four substances, tissue, whole blood, plasma and serum.
4 Am I right?

5 A. That would be?

6 Q. That you may be asked to test
7 for digoxin and be presented with one of those
substances?

8 A. Well, we can do that in those
9 substances, those matters, and we can do it in many
10 others.

11 Q. Before you perform an RIA or the
12 HPLC, do you use an extraction method?

13 A. Yes, generally, most of the time.

14 Q. Now, just to clear away another
15 thing. Do you use the extraction method with respect
to tissue?

16 A. Yes.

17 Q. Do you use it with respect to
18 whole blood?

19 A. Yes.

20 Q. Do you use it with respect to
plasma and serum?

21 A. Most of the time and the only
22 exception with respect to plasma or serum is if the
23 sample is so small, would be so small for it to be
done.

25



DD.8

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2 Q. But if given an adequate sample
3 of any of those substances you would use an extraction
4 method?

5 A. That is right.

6 THE COMMISSIONER: Just a moment, please.
7 I had understood the extraction method was the HPLC?

8 MR. SCOTT: No. I am just coming to
9 that.

10 THE COMMISSIONER: Well, let me
discover: what is this extraction method?

11 MR. SCOTT: That's my next question.

12 THE COMMISSIONER: Sorry. Go right
ahead.

13 MR. SCOTT: The question the Commissioner
14 asks is always better than the one the lawyer asks.

15 Q. You go right ahead.

16 A. The question is: what is
17 extraction?

18 Q. Yes.

19 A. I was under the impression I had
20 mentioned it before. The extraction is a mixing of
21 the blood or tissue with an organic solvent. In a
22 specific case in our analysis the organic substance
23 is dichloromethane and physically shaking the two
faces together with the anticipation and knowledge

24

25



DD.9

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2 because of the chemical nature of digoxin - digoxin
3 will leave the matrix of the blood and go into the
4 layer of the organic solvent. The organic solvent
5 layer can then be separated physically and evaporated
6 and an extract - the so-called extract is then used
on RIA or the HPLC aspect.

7

Q. If we take one of the liquids,
I take it what you are doing is you are extracting a
portion of that liquid. That is what extraction means,
is that correct?

11

A. Certainly you are extracting a
portion - a suitable portion of the blood.

12

Q. What is the purpose of doing that?

13

A. Well, the purpose is since most
of the time in forensic work we are dealing with
whole blood, the purpose is purification of some sort
to separate the drug from the crude matrix of the
whole blood or the tissue.

(2)

17

Q. Would it be fair to say as well
that it is a process designed to attain an adequate
sample on which to perform your tests?

20

A. That was part of the design.
This reason was taken into account.

22

Q. And that is called extraction?

23

A. The process of taking, yes, to
take, that's right.

25



DD.10

1

2 Q. And that is its purpose?

3 A. As I mentioned, that's right, yes.

4 Q. And that is done in every case

5 except perhaps for some serum cases where the sample

6 is not large enough. Is that what you said?

7 A. That is right or else in the

8 analyses of pure digoxin material which doesn't

require it.

9 Q. Well now, have you established

10 a recovery rate for your extraction process?

11 A. Yes, we have an average recovery

12 rate.

13 Q. May I just stop you there. You

14 have established a recovery rate. Just tell the

15 Commissioner and me by the bye what you say the

16 recovery rate is?

17 A. Okay. Thank you. The purpose --

18 Q. You don't have to look all the

19 way over to him. I want to hear you too.

20 THE COMMISSIONER: We are a little

21 better now. Apparently we did not have the three

22 microphones working but now we have this one working

23 so I can hear you without turning - not that I object.

24 I am rather glad when you turn my way but you don't

25 have to turn all the way.



DD.11

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2 MR. SCOTT: Do your best, Mr. Cimbura.

3 Q. What is the recovery rate?

4 A. That is right. The purpose to
5 study recovery is to find out how much of the drug
6 may be lost during the extraction process.

7 Q. Would you agree with me that the
8 establishment of a recovery rate efficiently is
9 absolutely critical to your ultimate test because it
tells you if your test is going to be accurate?

10 A. That is right. You wouldn't
11 want to lose everything. You want to have something
12 left. That's right.

13

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EE
EMT/cr

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2 Q. All right. Now will you
3 tell me and the Commissioner exactly what you mean
4 by extracting - I bring in a couple of grams of
5 tissue. You I think have told us that you then turn
6 it into a liquid in effect, is that correct, by
chopping it up and ---

7 A. Homogenizing it.

8 Q. Homogenizing it, all right.

9 And then you do an extraction?

10 A. Yes, that is right.

11 Q. Okay. Now what again is the
12 purpose of that extraction?

13 A. The purpose is to separate,
14 purification, to separate the drug from some of the
15 biological, naturally occurring biological material
16 in the blood or tissue.

17 Q. So what you are doing is you
18 are separating out a part of that homogenized substance
suitable for testing? Right.

19 A. Would you repeat that?

20 Q. What you are doing basically
21 is you are separating out a part of the homogenized
22 substance that is suitable and purified and proper
for testing?

23 A. Well, separating - during the

24
25



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2 extraction process - well, it depends. Separating
3 the digoxin from the quantity of tissue or blood that
4 is used for the extraction.

5 Q. All right. And the purpose of
6 the recovery rate is to ascertain whether you are
7 getting all the digoxin out or only part of it?

8 A. That is right. In a sense it
9 is to establish how much you are losing and whether
this is satisfactory.

10 THE COMMISSIONER: I thought the pur-
11 pose was to leave the digoxin in, not to take it out.
12 Have I misunderstood.

13 Q. Can you answer the question?

14 A. The purpose of extraction is
15 to separate, to take out the digoxin from the natural
16 components, you know, blood cells, for example, and
various material present in the blood and tissue.

17 THE COMMISSIONER: I understand that
18 part of it. I thought I understood it.

19 Q. Perhaps I can clear it up.
20 And the purpose of the recovery rate is to ascertain
21 the extent to which you have fully done that? Is
that correct?

22 A. That is right.

23 Q. Because if you show on your

24

25

RE-EXAM re extraction, recovery rate.
(see alc. p. 205)

Purposes of extraction process — refine, purify sample — get rid of blood components that not interested in testing?

You want to be sure that in the process you haven't lost the very thing you want to test for and measure — digoxin (Baby + bath water).

∴ determine recovery rate.

— how much ^{dry} ~~dig~~ have lost ($\%_d$).

— how much ($\%_r$) remains in refined sample

Different ways of expressing same thing?

Raccolle di ^(p. 208, e 17) uses Recovery rate = 85%

i.e. after extraction, 85% of dig
in measured sample remained
in refined sample

or (same thing) 15% of dig from
measured sample was "lost" (left
behind) in the extraction process.

* (see p 217 — have been explain)

[~~Rept of p. 206. Quizz 11] [P]~~



1

2 recovery rates that you are extracting only 50% of the
3 digoxin you are going to get a reading, for example,
4 that is half of what the real reading in the sample
5 provided to you should read?

6

A. That is right.

7 THE COMMISSIONER: All right. Can I
8 stop you. I am lost again. I thought the recovery
9 rate was to discover how much of the drug was lost in
10 the extraction process; now I seem to understand that
11 your purpose is to get it all out. The recovery rate
12 I take it is something, some kind of a test that you
13 make prior to the analysis of a tissue; is that
14 right?

15

16 THE WITNESS: Well, generally speaking,
17 sir, to do this we add a known amount of digoxin to
18 the blood, and following extraction we determine how
19 much is left. The difference is the loss due to
20 extraction.

21

22 THE COMMISSIONER: All right. A
23 leading question might help a lot.

24

25 MR. SCOTT: Q. Can I summarize it
this way: the purpose of the recovery rate is to
gauge the extent to which the ultimate substance that
you are testing contains for the purposes of the test
the same proportion of the toxic substance as the

RE-EXAM. Puzzled by answer.

READ lines 13-20.

"AND VICE VERSA"

Can't, in extract know recovery $> 100\%$
of the adj. in original sample.

If recover $< 100\%$ and don't make
any correction or take other steps
to compensate for loss, recorded level
will UNDERSTATE level in original
sample.

Can failure to compensate for loss in
extraction know even result in recorded
levels OVERSTATING level in original
sample?



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2 original material submitted to you? Isn't that right?

3 That is why you do a recovery study?

4 A. In my view this is what - this
5 is to determine how much one loses from the extraction
6 process, that is right.

7 Q. All right.

8 A. I believe this is the same ---

9 Q. I think we are saying the
10 same thing, but with lawyers, Mr. Cimbura, if you
11 haven't found out yet you will find out that we only
12 learn it if we can say it three times out loud, and
13 that is the exercise we are engaged in now.

14 So that the recovery rate is critical
15 because it is the gauge by which you measure whether
16 your ultimate reading bears any relation to reality?

17 A. Yes, from the sense that, of
18 course, if you lost a considerable amount then your
19 readings would be much smaller than they should be in
20 the original material.

21 * Q. Exactly. And vice versa?

22 A. That is right.

23 Q. And do you do recovery rates
24 for plasma, serum, whole blood and tissue in your
25 lab?

26 A. We have done recovery rates for



EE5

1

blood and tissue I believe as well.

2

Q. Have you done any for serum
or plasma?

3

A. No, I don't believe so.

4

Q. And when did you begin to do
recovery rates?

5

A. This was part of my evaluation -
it is a normal evaluation. It is a normal classical
standard evaluation method.

6

Q. All right.

7

A. In forensic toxicology work.

8

Q. Did you begin to get recovery
rates as soon as you began digoxin testing at the
Hospital for Sick Children, or was it later?

9

A. No, some time later.

10

Q. All right. How much later,
can you tell me?

11

A. I would have to go back and
consult my detailed notes on that.

12

Q. Well, we will be seeing you
again. Perhaps you can make a note to do that.

13

A. If I give you an approximation,
a time span, would that be satisfactory?

14

Q. That would be helpful, yes.

15

A. As I recall it, we began in -

16

17



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2 we began receiving samples in March, 1981, and some
3 time during the next three months the recovery was
4 studied as well as quite a few other parts.

EE6

5 Q. Now I understand that one of
6 the possible concerns with the extraction method is
7 that the recovery rate may vary from sample to sample?
Is that true?

8 A. It may vary from sample -
9 sample to sample of what? Of blood?

10 Q. Of blood or tissue or serum or
11 plasma. That it may vary from sample to sample, the
12 extent to which you get a 60% recovery or 40% recovery
13 or 80% recovery. "

14 A. It may, in my experience, and
in our work it may vary to a relatively small amount.

15 Q. To what degree?

16 A. I don't have the data available
here. Overall on the average our recovery rate was
17 in the order of 85%.

18 Q. Well, are you able to tell me
the extent to which the recovery rate may vary from
20 sample to sample in your experience?

21 A. At the present time I don't
have information with me.

23 THE COMMISSIONER: That is you have

24

25



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2 85% of the drug remaining after the extraction?

3 THE WITNESS: That is right.

4 THE COMMISSIONER: The recovery rate
5 is in order to determine the loss; the loss is 15%?

6 THE WITNESS: 15% on the average.

7 MR. SCOTT: Q. And I understand that
8 recovery studies are commonly used in labs to test the
uniformity of recovery rates over very many samples?
9 Isn't that your experience?

10 A. I'm sorry. Would you repeat
11 that?

12 Q. Yes. Recovery studies are
13 commonly used in labs to test uniformity of recovery
14 rates over many samples.

15 A. Well, they are usually evaluated
16 as part of the design of a method for a particular
sample.

17 Q. Right. Have you done any recent
18 studies?

19 A. Yes.

20 Q. All right.

21 A. Studied different samples.

22 Q. Is there any reason why that
can't be released to the Commission?

23 A. Release what?

24

25

EE7



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Q. Your recovery study. I would like to see it.

3

A. Well, I see no reason. It is subject to publication. Planning on publication.

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EE8

Q. That is fine. I don't want to interfere with that at all, but if you would be good enough at your earliest opportunity to provide a copy of any recovery studies you have done in this area to Mr. Lamek, he can then provide a copy to me. Will that be satisfactory?

A. If this is the direction of Mr. Commissioner, yes.

THE COMMISSIONER: Yes. There is no reason why you shouldn't?

THE WITNESS: No.

MR. SCOTT: Q. I am not going to publish it under my name, Mr. Cimbura, don't you be troubled about that, and I will see that nobody does at the Hospital, don't worry about that.

THE COMMISSIONER: I take it there is no objection to that.

MR. SCOTT: Q. Can you tell me now - I know you haven't got it before you but maybe you can remember - what was the sample size that you used in your recovery study?



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EE9

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A. I believe it was the same sample size as we used in the analysis of the cases which would be usually .5 millilitres of whole blood and less of tissue.

Q. I'm sorry, how many - what I meant when I asked the size of your sample was how many units were tested for uniformity?

A. I see. I don't recall that information.

Q. But that will be in your study?

A. Yes.

Q. I take it I will find in your study, just so I know we are talking about the same thing, your documentation of the study including the mean recovery rate, standard deviations and material of that sort.

A. Yes, I should hope so. I am not sure that I calculated the standard deviation, but I suppose if I find that it can be calculated from that.

Q. And do I have it right that you did the recovery study on tissue and whole blood?

A. As I recall it, yes.

Q. But not on plasma and serum?

A. As I recall it, yes.

Q. Do you know offhand if the



1

2 recovery study was done on diluted samples?

3 A. How do you mean diluted samples?

4 Q. What do I mean by diluted
5 samples? You told the Commission and I wasn't listening
6 that you do in fact dilute your samples. Is that
correct?

7 A. Yes.

8 Q. All right.

9 A. If it is necessary.

10 Q. Then we know what we are talking
11 about. Was the recovery done on the samples after
dilution?

12 A. As I recall it, it may have
13 been, yes.

14 Q. All right. Now you have made
15 me look like a fool but we got the same answer that
16 we wanted.

17 THE COMMISSIONER: Is this the
18 dilution because the reading is elevated.

19 THE WITNESS: Because the concentrations
20 would be over the calibration curve which requires dilutio

21 MR. SCOTT: Q. Have you done any
22 independent recovery rate studies apart from the
23 studies that were done with respect to patients in
the Hospital for Sick Children?

24

25

EE10

RE-EXAM : Explain this.

"in vitro" — in glass — i.e. not straight
actual human or animal samples or
tissue

Significance if any?

Purification

Why no in vitro samples.

(d) this study not have been done
on actual samples but for analytical)

— Braum there didn't know how
much drug received — as by bottom,
didn't know how much in animal
sample!

∴ start w. known concentration?

See what ^{to} received in extract
process.



EELL

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A. Have we done apart any recovery
studies with respect to what?

3

4

5

6

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8

Q. You have told us how important
the recovery rate is in testing the system. You have
told us how important, therefore, it is to do a study
in connection with it, and you have told us that the
samples from which you did the study were the samples
from the Hospital for Sick Children.

9

10

What I am asking you is have you done
any studies on your recovery rate on other samples?

11

12

13

14

A. These recovery studies were,
as I recall it, done mainly on what I call in vitro
samples. These are samples of blood to which digoxin
is added. These were not necessarily samples from any
particular children.

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- - - - -

RE-EXAM.

Re correction

Purposon of correcding wd be to compensate
for the loss of dig which recovery rate
shows to have been lost in extraction process.

Scott's example if only recovered 50%

- [Student you didn't use subtract^s losses w.
only 50% recovery rate?]

Thnk if only 50% recovery, wd get
actual ^{R.I.A.} reading on refined sample of
say 4 mg/ml. — if chose to do a
"correction" wd say "But I know my
recovery rate is only 50%, therefore I
have measured only $\frac{1}{2}$ the dig that
was originally in the sample. ∴ to
get true loss in original sample, multiply
reading by 2 = 8 mg/ml in original sample
or avg. recovery rate c. 85%.

If do not make "correction" to compensate
for loss of 15% AND if take no other
measures to compensate for that loss,

follow that recorded loss from R.I.A.
of refined sample will be
UNDERSTATED as loss in
original sample?

How else cd you compensate for
known loss in extraction process?

You do that in sp. lab?

[Go BACK TO P. 206, l. 13] *



/BB/ak

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Q. Now, I take it that when you have an extraction sample and have done a recovery rate for it, you make a correction, don't you?

A. No, we haven't corrected for the 15% on the average for the last, in our results.

Q. All right. Do any of your results reflect a correction?

A. Which results are we referring to now?

Q. We're talking about the samples that you have taken since March of 1981.

THE COMMISSIONER: It doesn't mean a great deal if we don't know what they are and we won't get those until later.

MR. SCOTT: Well, no, I'm talking about his method now. The problem is that his method has been tested - I shouldn't say tested in a pejorative sense but it has been utilized only in connection with this incident. So, if we're going to talk about his method we are inevitably going to get to this case.

THE COMMISSIONER: I understand that but whether he has used it or not will not really make an awful lot of difference until we have the figures, that's all. If the figures are



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10,000, whether he's taken 15% in or not.

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MR. SCOTT: I'm not asking for the figures, Mr. Commissioner, I'm asking at what level -- let me put it this way.

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THE COMMISSIONER: It's easier to have the question that to argue about it.

7

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MR. SCOTT: Q. At what level did you begin to apply a correction? At what recovery rate do you begin to apply a correction?

9

10

THE COMMISSIONER: If you do at all.

11

12

MR. SCOTT: Q. Yes, if you do at all.

13

A. Well, I think there is a misunderstanding here.

14

Q. Do you want me to try again?

15

Perhaps I haven't made myself clear?

16

A. Yes, I'm having difficulty.

17

Q. All right. We have been this

18

far that when you do this extraction, before you even get to the RIA, one of its purposes, perhaps it's only purpose is to ascertain the extent, the amount of digoxin from the whole that you are taking out or the amount that you are leaving behind, right?

21

A. Yes.

22

Q. And that we then do a recovery rate to find out the proportion, and you may get

23

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2 50%, you may get 100%. You told me that many of your
3 cases were in excess of 80%.

4 A. Yes.

5 Q. An 80% extraction, is that
6 right?

7 A. 80% extraction.

8 Q. Well, isn't that what you
9 said, an 80% recovery rate?

10 A. I said our average was about
11 85%.

12 Q. And if your average was 50%,
13 I take it you would make a correction by virtue
14 of the fact that you had only extracted 50%.

15 A. Yes, one could make a correction
16 and should make a correction or else one should, you
17 know, do the methodology in a different way. One
18 can calibrate the standard curve following extraction
19 from the sample, which would compensate for whatever
20 extraction losses you were having.

21 Q. Well, my question to you is,
22 bearing in mind that you had some recovery rates
23 that were less than 100%.

24 A. Yes.

25 Q. Did you ever make a correction?

26 A. Well, we had such a complexity



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of samples that were examined that I cannot recall
using any correction.

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THE COMMISSIONER: Well, when you come back I would think that would be of some importance. When you come back you can consider it because that's one of the questions that will be asked.

THE WITNESS: Okay, I will look it up.

THE COMMISSIONER: Right.

THE WITNESS: But we had such a multiplicity of samples.

MR. SCOTT: Q. I take it it might be possible for you to ascertain the correction rates if any you used and give them to the Commission Counsel at the same time you are giving him your recovery rate studies. Would that be possible?

A. Well, I would prefer to do it when I come back when I have a chance to review all the results which I really haven't done up to now, if this is satisfactory?

MR. SCOTT: Well, I'm in the Commissioner's hands.

THE COMMISSIONER: Certainly if we



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get the information beforehand. Mr. Lamek, you are
nodding your head, we will pass it on.

4

MR. LAMEK: Yes.

5

6

MR. SCOTT: Q. There's no difficulty
about letting us have the recovery studies right
away?

7

8

A. Pardon me?

9

Q. There's no difficulty about
letting us have the recovery studies?

10

11

12

13

A. Well, other than have been
carried out over two years ago and in locating the
information and seeing whether it is still available
still and so on.

14

Q. All right.

15

THE COMMISSIONER: We're going to
rise in a few minutes anyway, is this a good time?

16

17

MR. SCOTT: Well, I can carry on
for a few minutes if you would like me to.

18

19

THE COMMISSIONER: Well, I just
was wondering.

20

21

MR. SCOTT: I'm going to be about
20 more minutes.

22

23

THE COMMISSIONER: Well, we might
as well take 15 mintues now then.

24

---Short recess.

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---Upon resuming.

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THE COMMISSIONER: I hope that all that

standing was for the purpose of exercising your legs,
it is not part of the procedure here. The only
person who has to stand unfortunately, Mr. Scott,
is you.

8

MR. SCOTT: Yes.

9

THE COMMISSIONER: That hardly seems
fair, but that's the rule.

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MR. SCOTT: Q. Mr. Cimbura, if you
can just be patient with me for a minute about these
recovery studies. I'm told that this might be a
suitable recovery study, that you took, let us say
10 samples of whole blood from 10 different patients,
that you divided those samples into three - you
divided each of those 10 samples into three parts
and you injected each of those parts with three
different levels of digoxin so that you would have
10 parts which would have low level injection of
digoxin, 10 parts that would have, say, medium level
injection of digoxin, 10 parts that would have
heavy injections of digoxin representing the blood of
10 different people, and that you then measure your
recovery rate of that digoxin. Do you understand
what I'm talking about?



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A. Yes.

2

3 Q. Yes. Is that the kind of
4 study that you did?

5 A. As I mentioned, I don't
6 recollect exactly what was done.

7 Q. I see. But your study will be
8 made available?

9

A. Yes.

10

Q. But I take it that you didn't
do that on serum and plasma?

11

12 A. As far as I recall right now,
yes.

13

14 Q. Yes. I don't want to get into
the actual samples, but I take it we can agree that
15 almost half of the samples you got were plasma and
serum samples?

16

A. Samples from where?

17

18 Q. From the Hospital for Sick
Children and from the bodies of patients that had
been there.

19

20 A. No, I don't think so. Again,
I would have to go in detail of what was received
21 but I don't think I would agree with that at all.

22

23 Q. All right. Well, we'll find
out in due course, thank you.

24

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Now, do you know what the expression
'a between day precision check' means?

4

A. Between day precision check?

5

Q. Yes, have you heard that

6

expression?

7

A. Yes.

8

Q. I see.

9

A. Perhaps not in exactly the same
words but the expression I usually heard is inter-
assay variation precision study, yes.

11

12

Q. Well, it's recognized is it not
that in any laboratory setting the test results
received may vary from one day to the next for minute
reasons that have nothing to do with the object being
assay. Isn't that true?

15

16

A. There may be some variations,
that's right.

17

18

Q. Have you done a study designed
to reveal, in your laboratory, the variations that
occur to date that occur from day to day in your
testing?

21

22

A. As I recall it, we have done
some of it on some specimens. Again, I don't have
the details with me right now.

23

24

Q. Would you have a report that

25



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you could show us that would let me see to what extent or what that study has revealed?

4

5

A. I don't have the report with me.

6

Q. No, but you can give it to Mr. Lamek.

7

8

A. If I can find it, yes.

9

10

Q. Thank you. Can you tell me just without referring to it how that precision study was done?

11

12

A. I'm not still sure. Are you referring to both inter-assay variation, precision or what?

13

14

Q. I'm told, and correct me if you don't agree with me, that every lab has the experience of a daily variation in the results that it gets when it tests and that as a result a lab does a precision study to determine the extent of that variation in order, if necessary, to correct its results or to control them. Are you familiar with that?

20

21

A. Well, I am familiar with the term. The variations with respect to - you are referring to RIA procedure, are you?

22

23

24

25

Q. Yes, any procedures you perform

RE-EXAM

Details and study notes (if available) conq
but. in principle, EXPLAIN how use of
standards and calibration curves operate
as a quality control or precision device.

Q.V. — [Same as p. 225, line 5 — application
of analyses — EXPLAIN]



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in your lab.

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A. The variations are usually controlled by running controls with the RIA and as well as running a calibration curve with each particular assay. Is that the type of variation that you have studied, that you are asking me to?

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Q. I'm told they are usually called between day precision checks, but if they're not I've asked you about that and you have undertaken to let me have what you have on that subject. I want to go further and say if that term isn't familiar to you, have you done any studies about internal quality control of your results in the lab?

A. By using a calibration curve.

Q. By using any method, have you done internal quality control to gauge the extent to which your results from day to day may vary?

A. Well certainly, yes. We are doing, as I mentioned previously, we're doing a calibration curve with standards with each assay.

Q. Well, I'll be coming to the standards on the assay in a moment, but are you and I talking about the same thing? You are familiar with the phenomena, I think you've told us, in which a lab gets different results from day to day.



A. Yes, the intra-assay variation is studied to a large extent when one develops a new procedure. We have done some of these evaluations and I cannot really recall right now what exactly was done, but as far as guaranteeing the quality of control or results, yes, this is done with each assay, a standard of calibration control is being run and controls are being used in the RIA assay.

Q. Do you do then, if I have it right, precision studies for the RIA?

A. Yes, I believe we have some, yes. I'm not exactly sure whether it will be what you are referring to but we have done some, yes.

Q. Do you do precision studies for the HPLC?

A. Yes, we have done some studies.

Q. Do you do precision studies for the utilization of plasma whole blood serum and each kind of tissue that you're testing with respect to that equipment?



G G
JC/cr

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A. Do we do what?

2

Q. Do you do precision studies
for example, each fluid?

3

A. Well, to begin with each fluid
is analysed in duplicate, at least in duplicate some
idea of the precision can be gathered routinely from
the extent of the duplicates in each analysis.

4

By duplicate meaning twice.

5

Q. I just want to leave that.

6

I take it you will be in a position after a period
of time to provide copies of that material, if not
the originals, of those tests to Mr. Lamek?

7

A. Well, I will attempt to do
whatever I find, whatever was done, and if it is
relevant and he has to do that, yes, that is right.

8

Q. Well, I know you will allow
Mr. Lamek to decide if it is relevant?

9

A. Yes, certainly.

10

Q. If you can find that, I would
much appreciate having it.

11

A. Well, as you know, precision
is a big word and as I mentioned when you are analyzing
results by duplicate analysis and in some case by
triplicate analysis, they are precision studies.

12

Q. And precision studies in your

13

14

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GG.2

JC.jc

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2 lab are critical, are they not, to be sure that the
3 results you give out --

4 Excuse me just a moment.

5 MR. SCOTT: I am sorry.

6 MR. LAMEK: I know that Mr. Cimbura
7 would do what he can to comply with that request but
8 it seems to me there may have been rather a breakdown
9 in communications as to just what it is that is being
10 asked for. Precision studies does not seem to be a
11 term that Mr. Cimbura ^Would use and I wonder if Mr.
12 Scott could make absolutely plain what it is he wants
in order that Mr. Cimbura may do his best to comply.

13 THE COMMISSIONER: That could be done
14 by mail.

15 MR. SCOTT: Well, I don't think I can
16 make it any plainer than I have. If he has done any
17 precision testing or quality control testing on his
18 lab or study testing at the lab or in any of the
19 equipment or in variations that may appear from day
to day, I would like the opportunity to see that
because as you can imagine, a great deal depends upon
it.

20 Q. You understand that, Mr. Cimbura?

21 A. Yes, and I have mentioned some
22 of the quality controls that we have been doing.

23

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GG.3

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2 Q. Thank you very much. Now let me
3 go happily to another matter. You have told the
4 Commission that you used an antibody in the RIA test
5 and you described that?

6

A. That is right.

7

Q. I am told that the specificity
of different antibodies varies. Do you agree with that?

8

A. It may vary.

9

THE COMMISSIONER: It may make a
10 tremendous difference but I have not the faintest idea
11 what it means.

12

MR. SCOTT: Q. Well, tell the
13 Commissioner because he wants to understand this like
we do what that means. The impact of specificity.

14

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A. Well, specificity in my view is
the ability of the antibody to distinguish a specific
compound such as a digoxin depending on how the
antibody synthesizes and made available and it is
my understanding that there may be variations in
the specificity and to the degree with which some
substances may cross react with any particular antibody.

21

Q. The more specificity the more
binding with the chemical or substance?

22

23

24

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A. Well, the more specificity the
more individuality by the antibody to bind only with
one substance.



GG.4

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2 Q. So if there may be a variation
3 in the specificity I take it that there may also be a
4 variation in the digoxin specificity in antibodies?

5 A. This is what I understood from
6 previously.

7 Q. And that specificity particularly
8 with respect to digoxin will vary from manufacturer
9 to manufacturer of the antibody?

10 A. Presumably.

11 Q. So that antibodies may be more
12 or less specific to digoxin with the less specific
13 antibody picking up or binding with more molecules
14 which are not digoxin. Is that not right?

15 A. The different antibodies may
16 have different -- somewhat different crossing activities
17 to different substances, that's right.

18 Q. Where do you get the antibodies
19 you use for the tests in connection with the Hospital
20 for Sick Children deaths?

21 A. As we mentioned previously
22 these are ordered from Beckman Company.

23 Q. You do not produce them in other
24 words. You buy them?

25 A. That's correct, sir.

Q. Have you ever tested them for
specificity?



GG.5

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2 A. We have tested them for cross
3 reacting to some of the known compounds that are
4 known to cross react with digoxin.

5 Q. Yes. Have you tested them for
6 digoxin specificity?

7 A. I am not sure what you mean.

8 Q. Well, for example --

9 A. We have studied the cross
10 reactivity to the antibody of some different drugs.

11 Q. Have you, for example, ever added
12 digitoxin to see if it cross reacts with your antibodies?

13 A. Yes, we have and to what degree.

14 Q. Do you have reports of that?

15 A. Yes, it was done and the infor-
16 mation was available. I hope it is available.

17 Q. All right, because you know what
18 I'm going to ask you about it, don't you. Can I
19 have it? If you can find it have you done the same
20 thing for digitoxin?

21 A. I am not familiar right now with
22 the term.

23 Q. Have you --

24 A. It may be under another name.

25 Q. You have told us about digitoxin.
26 Have you tested for any digoxinlike substances?



GG.6

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2 A. Yes. As I recall we have tested
3 for a number, the cross reactivity of a number.

4 Q. Can you let me know the names
5 of those and if you can find them the results of the
6 tests?

7 A. Yes, sir.

8 Q. Let us go to the HPLC. I under-
9 stand from what you said this morning that the purpose
10 of that method is to separate the pure digoxin from
11 the metabolites and other drugs or thirdly digoxinlike
12 substances. Have I got that right?

13 A. I am sorry, I was making notes.

14 Q. I am sorry. Let us go to the
15 HPLC. I understand from what you said this morning
16 that the purpose of that method is to separate the
17 pure digoxin from the metabolites and other drugs and
18 digoxinlike substances. Is that right?

19 A. Yes, from metabolites, other
20 drugs and hopefully from other digoxinlike substances.
21 It is hard to be specific there because we don't know
22 what these other substances are.

23 Q. I take it the HPLC produces a
24 sort of graph with points in it?

25 A. Yes, you can produce a graph on it.

Q. Is that how it is done in your
lab?



GG.7

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2 A. Do you want me to explain what
3 is done in our lab?

4 Q. I would like you to tell me if
5 you can if it is done in graph form in your lab; if
6 it produces readings that shows points on it?

7 A. We have a calibration card done,
8 yes, and in some instances we have used other graph
9 forms, depending on what we want to study with it.

10 Q. I take it you use standards to
11 identify or to separate the substances out?

12 A. We use standards for calibration
13 curves.

14 Q. But the standards are used for
15 calibration curves so that you can say this curve is
16 pure digoxin, this curve is Metabolite No. 1 and this
17 curve is Metabolite No. 2. Is that right? And you
18 can separate them out in that fashion?

19 A. That is right. You need a
20 standard drug to be able to compare it to your
21 analytical results.

22 Q. You need a standard to tell you
23 which is Metabolite 1 and which is digoxin, don't you?

24 A. That's right.

25 Q. And those standards exist?

A. That is right.



GG.8

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Q. And you use the readily available
standards?

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A. That is right. Some are pretty
difficult to get.

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Q. Now, I am suggesting to you,
Mr. Cimbura, that at the present time, and as one of
the great challenges of science, that at the present
time standards exist for digoxin, metabolite and a
number of other drugs?

10

A. That is right.

11

12

Q. But that today there are no
standards for unidentified other digoxinlike substances?

13

A. That is correct.

14

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Q. Well now, how do you pick them
out on your HPLC in order to exclude them if there
are not any standards?

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A. I cannot pick standards to
exclude these since the identity of those terms is
unknown.

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Q. So if the calibration curve from
your HPLC, which you have identified as the digoxin
curve, according to the digoxin standards, is the same
as the curve produced by the digoxinlike substances,
you cannot separate one from the other, as a practical
matter?



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A. If it is I think it will be based on my experience with this technique. As I mentioned before I am satisfied reasonably that it's not.

Q. How do you separate --

THE COMMISSIONER: It is not what?

THE WITNESS: I am reasonably satisfied, Mr. Commissioner, that what we are separating from the HPLC column is digoxin but in theory certainly there is a possibility that some other substance may have identical retention time on the HPLC column. I would however feel it is unlikely but it is a possibility.

MR. SCOTT: Q. Whether you or I feel *it* is unlikely, *is* absolutely unknown, is it not. I mean I might as well say it is likely. Nobody knows. Isn't that right?

A. Well, nobody knows what those substances are.

Q. If you can't identify the substance then you can't tell where it appears, can you?

A. No, you cannot.

Q. And if you cannot tell where it



GG.10

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2 appears you cannot exclude it in order to get a pure
3 digoxin reading. Is that not fair?

4 A. Well, you cannot exclude them
5 absolutely but I believe that you can exclude them
6 based on my experience and by doing various
7 modifications to a reasonable degree of scientific
certainty.

8 Q. Will you just tell me what you
9 do to exclude these unidentified substances in cases
10 where we have no standards to judge them? Just tell
11 me what you do to exclude them so you can certify that
12 what you get from the HPLC is true digoxin?

13 A. As I mentioned you cannot
14 absolutely exclude them. However, by doing various
15 variations of the HPLC such as using different column
16 conditions, doing the HPLC analyses in a reverse mode
as well as a normal mode.

17 Q. I don't want to interrupt you
18 but I just want to be sure we are talking about the
19 same thing. Would you be good enough to tell me all
20 the things that you have done that justify your saying
21 in your opinion to the Court that you have likely
22 excluded digoxinlike substances? Just give me the
names even though they won't mean anything to me?

23 A. Yes, we have done almost if not

24

25



GG.11

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2 all specimens where it has been possible, we have done
3 the regular approaches that I have described previously.
4 In two of the specimens from two of the children in
5 addition to this regular approach other analytical
6 approaches were done and I believe I mentioned it
7 previously. In the case of one child in addition to
8 the regular approach we have also employed mass
spectroscopic coupled with the gas chromatography.

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EMT.jc
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Q. And you did that with respect to a sample from one child?

A. From one child, that is right.

Q. All right. That is one thing you did. Will you tell us anything else you did that led you to conclude with a fair degree of certainty as I think you have that what you were getting was pure digoxin from the HPLC? What other test?

A. In other specimens from another child which we have in addition again to the regular approach that was already described we have used another different column in the reverse phase, mode, of the HPLC.

THE COMMISSIONER: Another different column?

THE WITNESS: Another column.

THE COMMISSIONER: Yes. In what?

THE WITNESS: In the reverse phase or reverse mode of the HPLC analyses, and in addition to that, in the same phase, we have also used another column still in the normal phase of the HPLC analyses.

In addition to that we have still used in this one instance another antibody that was used by another company to perform the other RIA analyses, and I was satisfied with the results obtained in all these.



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Q. Now you have told me about three other tests you performed in conjunction with the HPLC to exclude readings for digoxinlike substances?

A. To give me additional certainty --

Q. Yes. All right.

A. -- in my opinion that I am dealing with digoxin.

Q. Did you do anything else or have you covered it?

A. Yes, I believe, as I recall it right now, yes.

Q. Yes. Now did any of that produce notes or reports or studies or documentation?

A. Yes.

Q. And do you have that as well?

A. Yes, I should have it.

Q. Yes. Thank you. Would you be good enough to provide that to Mr. Lamek?

Now just a couple of questions again about the RIA and the HPLC.

A. Excuse me for a moment. Sorry.

Q. Now, if you are going to do an RIA test I take it you in effect get a kit from Beckman?

A. Yes.



HH.3

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Q. Does that kit have values

3

attached to it?

4

A. You mean monetary values?

5

Q. Well, no, standards.

6

A. Yes. Oh, yes, it has standards.

7

Q. And will you tell the

8

Commissioner what that is. What they are? Describe
them.

9

A. Yes. These are part of the kit
or package and contain, as I recall it, standards of
varying concentrations of digoxin ranging from, when
reconstituted properly, ranging from .5 nanograms
per millilitre.

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Q. And how do you use those standards
in the testing process?

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2 he wants to understand how you use those standards.

3 What are they for?

4 A. As I have mentioned previously
5 they are to produce a calibration curve.

6 Q. Yes.

7 A. Which is used for calculating
8 of the concentration of any unknown sample with respect
9 to digoxin.

10 Q. Yes, all right. And how is that
done?

11 A. This is done by carrying the
12 standards through the same procedure as the sample is
13 being carried through.

14 Q. Yes.

15 A. And the readings are tabled in a
calibration curve.

16 Q. And then you take your reading
17 and apply it to the standard and get the results; is
18 that it? Have I got that right?

19 A. You run a standard through and
20 for each standard, of course, you get a reading in
21 terms of per cent binding of digoxin to the complex,
22 and then you combine those in a calibration curve and
23 they range between .5 nanograms per millilitre to 6
nanograms per millilitre as was described previously.

24

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HH.5

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2 Q. Yes. And you told the
3 Commissioner that somewhere along the line in the
4 process you decided to use your own standard?

5 A. That is right. Actually before
6 we began the application for the case specimens.

7 Q. I beg your pardon?

8 A. As I told you before this was
9 before we began to apply our methodology to the
specimens involved in this investigation.

10 Q. And do you then assign the
11 Beckman values to your standards?

12 A. No. We assign our standards, the
value of our standards.

13 Q. All right. So having developed
14 your own standards you don't assign them to the
15 Beckman values at all, assign the Beckman values to
16 them?

17 A. I really don't know what you mean?

18 Q. All right. As long as I am clear
that you don't --

19 A. I don't know what you mean by
assign them to Beckman values.

20 THE COMMISSIONER: I just don't under-
stand the distinction between values and standards.

21 MR. SCOTT: Q. Well, excuse me. Do

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2 you have standards for serum and for saline?

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4 A. We have, yes. We have the
5 standards that come commercially available from
6 Beckman. Yes, we have standards - our standards are
in saline that we use for our procedure.

6

7 Q. Is the recovery the same for
8 saline as it is for tissue? I'm sorry, for serum as
it is for tissue?

9

A. The extraction recovery?

10

Q. Yes.

11

12 A. I don't believe I ~~studied~~
extraction recovery for serum.

13

14 Q. Isn't the issue that if the
standards are not the same for saline on the one hand
and serum and tissue on the other, that then they won't
15 produce the same curve?

16

17 A. Well, the reason - one of the
reasons why we went to saline standards is because
18 the majority of our work in forensic work required dilu-
tion with saline so that they are best comparable
19 to standards in saline.

20

21 Q. Well, we will pursue this later
perhaps.

22

Excuse me, Mr. Commissioner.

23

I take it, Mr. Cimbura, that if one

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2 understood your testing method one should be able to
3 duplicate your results?

4 A. Yes.

5 MR. SCOTT: Thank you very much.

6 THE WITNESS: A properly trained person.

7 MR. SCOTT: Oh, of course. I am not
going to do it.

8 Thank you very much.

9 THE COMMISSIONER: Thank you, Mr. Scott.

10 Mr. Bogart?

11 MR. BOGART: Mr. Commissioner, I wonder
12 if I might through you ask that Mr. Lamek provide
13 copies of the studies that Mr. Cimbura is going to
14 produce for Mr. Scott to me, or if that is too
15 difficult, at least notify me when Mr. Cimbura has
16 produced them to him so that I at least may have an
opportunity for inspection.

17 THE COMMISSIONER: Yes. That means
18 more work for the copying machine I guess.

19 MR. BOGART: What I am saying, Mr.
Commissioner, is I would at the very least like to be
20 notified that the studies and the documentation are
21 available.

22 THE COMMISSIONER: Yes.

23 MR. BOGART: For inspection.

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2 THE COMMISSIONER: Yes.

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THE COMMISSIONER: Now whether Mr. Lamek

will be kind enough to provide me with actual copies,
I may have to leave that to his good graces.

THE COMMISSIONER: Yes. All right.

We have got a large body of people that seem to be
doing nothing but attending upon that copying machine.
We have even got a new copying machine at Her Majesty's
expense so maybe we will be able to provide all this.

MR. BOGART: Yes. Thank you very much.

CROSS-EXAMINATION BY MR. BOGART:

Q. Mr. Cimbura, my cross-examination
I think will follow perhaps more closely the testimony
you have given this morning, and I would like to start
at the beginning of your examination when you said
that prior to your beginning to do analyses in March
of 1981 on the samples that came from the Hospital
for Sick Children you were generally familiar with
digoxin analysis but not to any degree.

Have I got that correct?

A. What I intended to imply is that
I was generally familiar with the drug digoxin.

Q. Yes.

A. I studied that in school and I
read up some literature about it.



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2 Q. And you may even have done one
3 or two tests a long time ago? You told that to Mr.
4 Scott.

5 A. Yes, but we had no personal
6 experience with the methodology that was necessary for
7 the analyses.

8 Q. You had no experience?

9 A. With this particular methodology
10 that was described previously, that is right.

11 Q. Did you have a knowledge about
12 the methodology? Did you know how to go about it?

13 A. Well, yes, I had general knowledge.
14 As I had mentioned RIA's, for example, are used for
15 other drugs in addition to digoxin.

16 Q. Yes, I know, but with respect to
17 digoxin?

18 A. I may have had knowledge about
19 digoxin, RIA being used for digoxin. It is hard for
me to think two years back and finding out exactly
what I knew or not.

20 Q. Well --

21 A. But I probably was aware that RIA
22 was one of the techniques that is quite commonly used
23 for digoxin analyses in body samples - in serum and
24 plasma, yes.

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Q. And that is, of course, because RIA is a commonly used method of analysis for many drugs, is it not?

A. For many drugs, that is right.



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Yes. So, do you do anything though specifically to inform yourself of what the appropriate techniques concerning the methodology and analysis of digoxin?

A. Prior to 1981?

Q. Yes, prior to your starting in March of 1981.

A. No, nothing specific.

Q. No, nothing specific, okay, thank you.

Now then, when you were responding to a question from Mr. Lamek, you said that there were some difficulties in respect of the detection and measurement of digoxin the blood, and I think that in fact you detailed two of the difficulties.

Now, the first difficulty was that the dosage of digoxin is quite small because digoxin is a potent drug. Have I got that correct?

A. Yes I recall that, yes.

Q. Now, you said that was the difficulty in terms of detection and measurement of digoxin in the blood. Will you just tell me what makes that a difficulty.

A. Well, one of the limitations of any analytical technique is the limit of detection



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which means the amount of substance that you can
detect.

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Q. And I take it that the smaller
the amount of the drug in the blood the more difficult
it is to detect, the more difficult it is to do these
analysis and detection?

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A. Well, I think what I want to
imply is that some techniques are just not capable
to measure the extremely low concentrations in blood.

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A. Well, I think what I want to
imply is that some techniques are just not capable
to measure the extremely low concentrations in blood.

Q. So, you are limited in the

techniques you can use to detect and analyse digoxin
in the blood?

A. That's right.

Q. Because you have given such
a small dose?

A. That's right, because with the
result that the levels in the blood are very small.

Q. Yes. And then the second

difficulty that you told us about was the fact that
digoxin has a high molecular weight?

A. Yes.

Q. I just want to refresh your
memory. What's the significance of digoxin having
a high molecular weight?

A. This was in reference to using



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2 one of the sophisticated techniques, mass spectrometry
3 coupled with gas chromatography.

4 Q. What's the significance of that?

5 A. The significance there was that
6 that property, together with other properties of
7 digoxin make it difficult for the drug to be analysed
8 by that technique, which is a very sophisticated
technique.

9 Q. So, that's not a technique that
10 you use, is it?

11 A. We used that in one instance.

12 Q. Yes. You did use it in one
13 instance, you told Mr. Scott about that this afternoon,
14 didn't you?

15 A. Yes.

16 Q. So, in fact, there are some
17 instances where you have used mass spectrometry and
18 gas chromatography, if I am pronouncing it right?

19 A. Mass spectrometry coupled with
20 gas chromatography, that's right.

21 Q. Yes. And what are the advantages
22 of that test?

23 A. Well, mass spectrometry, I would
24 consider that very sophisticated instrumentation which
25 increased the probability of any identification of any



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2 drug if it's positive.

3 Q. Well, but you said so that's
4 the advantage but because digoxin has a high molecular
5 weight, it is difficult to use this test, I take it,
6 because that's what you told us this morning.

7 A. Among other factors combined
with it, that's right, yes.

8 Q. I see. But at least in one
9 instance you thought it was a problem to use it?

10 A. Well, it was tried in that
11 test and the application was studied.

12 Q. Yes.
13 A. And evaluated and it gave us,
14 it was very time consuming because of particular features
of that one case and it was possible to get positive
results.

15 Q. And you felt you got a good
16 reading from that test that you used a desirable one
17 and an appropriate one?

18 A. We had a positive finding for
digoxin.

19 Q. Yes, okay, thank you.

20 Now then, when you were describing
21 the RIA, you said that while it was a good test, it
22 had some disadvantages, and if I've got your testimony
23 correct, you said that one of the disadvantages of RIA

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2 was that that chemical like digoxin, digoxin like
3 chemicals can cross react with substances used for
4 the RIA test?

5 A. Yes.

6 Q. And we heard more about that
7 when Mr. Ortved examined you and then I believe Mr.
8 Scott had something to say about it as well.

9 But if I've got your testimony correct
10 from this morning, you said that, in your opinion, the
11 RIA nevertheless remained a good test so long as
12 people know what drugs have been administered. Have
13 I got that right?

14 A. Yes, I think it's a good
15 screening test for digoxin.

16 Q. It's a good screening test for
17 digoxin?

18 A. Yes.

19 Q. So long as people know what
20 drugs had been administered?

21 A. Well, that certainly would
22 tend to minimize the disadvantage that one knows
23 what drug is administered. That's the drug that
24 you would expect to find.

25 Q. Well, for example, I take it
26 that it wouldn't tell you anything about other drugs





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II6 2 that had been administered, would it?

3 A. Other drugs such as, sir?

4 Q. Pardon me?

5 A. Other drugs such as?

6 Q. Oh, well, it would tell you
about other drugs?

7 A. Well, it might, as I mentioned,
it can cross react with some digoxin like drugs.

9 Q. But supposing another drug had
10 been administered, excluding the digoxin like drugs
11 that you listed this morning.

12 A. Yes.

13 Q. What were they? They were
14 digoxin and deslanoside ... and lanatoside C and things
like that.

15 A. Yes.

16 Q. Would it tell you about any
17 other drugs?

18 A. Would it tell you what?

19 THE COMMISSIONER: You mean ones like
cocaine or that sort of thing?

20 MR. BOGART: Well, would it tell you
21 whether any other drug had been administered?

22 THE COMMISSIONER: Well, any non-digoxin
23 like drug, is that what you mean?

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2 MR. BOGART: Yes, any other non-digoxin
3 like drug. Thank you, Your Lordship.

4 THE COMMISSIONER: Well, it surely
5 couldn't if you were comparing it with digoxin, it
6 wouldn't be an awful lot of help, would it?

7 MR. BOGART: No, I wouldn't have thought
8 so but I would appreciate if this witness could tell
us that.

9 THE WITNESS: Well, I think it is such
10 a general question that I haven't seen any drug other
11 than digoxin like in some way drug so that I wouldn't
12 expect it to tell me anything about any other drugs.

13 Q. But you don't really know.

14 THE COMMISSIONER: Well, I'm sorry,
15 but just taking a radical example, would it tell you
whether cocaine was in the body or not?

16 THE WITNESS: No, I wouldn't expect
17 it, Mr. Commissioner.

18 THE COMMISSIONER: I would be stunned
19 if it did. Perhaps it will, will it. I mean, I don't
20 know, but I wouldn't think that when you're comparing
it with a sample of digoxin it would help you much.

21 THE WITNESS: That's right.

22 THE COMMISSIONER: It wouldn't tell you
23 much about cocaine or opium?

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1 THE WITNESS: No, I wouldn't expect
2 it to. But I haven't actually tried cocaine, let's
3 say, to put under these conditions of the assay.

4 THE COMMISSIONER: Yes.

5 THE WITNESS: But I would not expect
6 it to show up. There is a separate antibody for cocaine.

7 MR. BOGART: Q. Are you familiar
8 with a drug called betablocker?

9 A. There's a group of drugs,
10 yes.

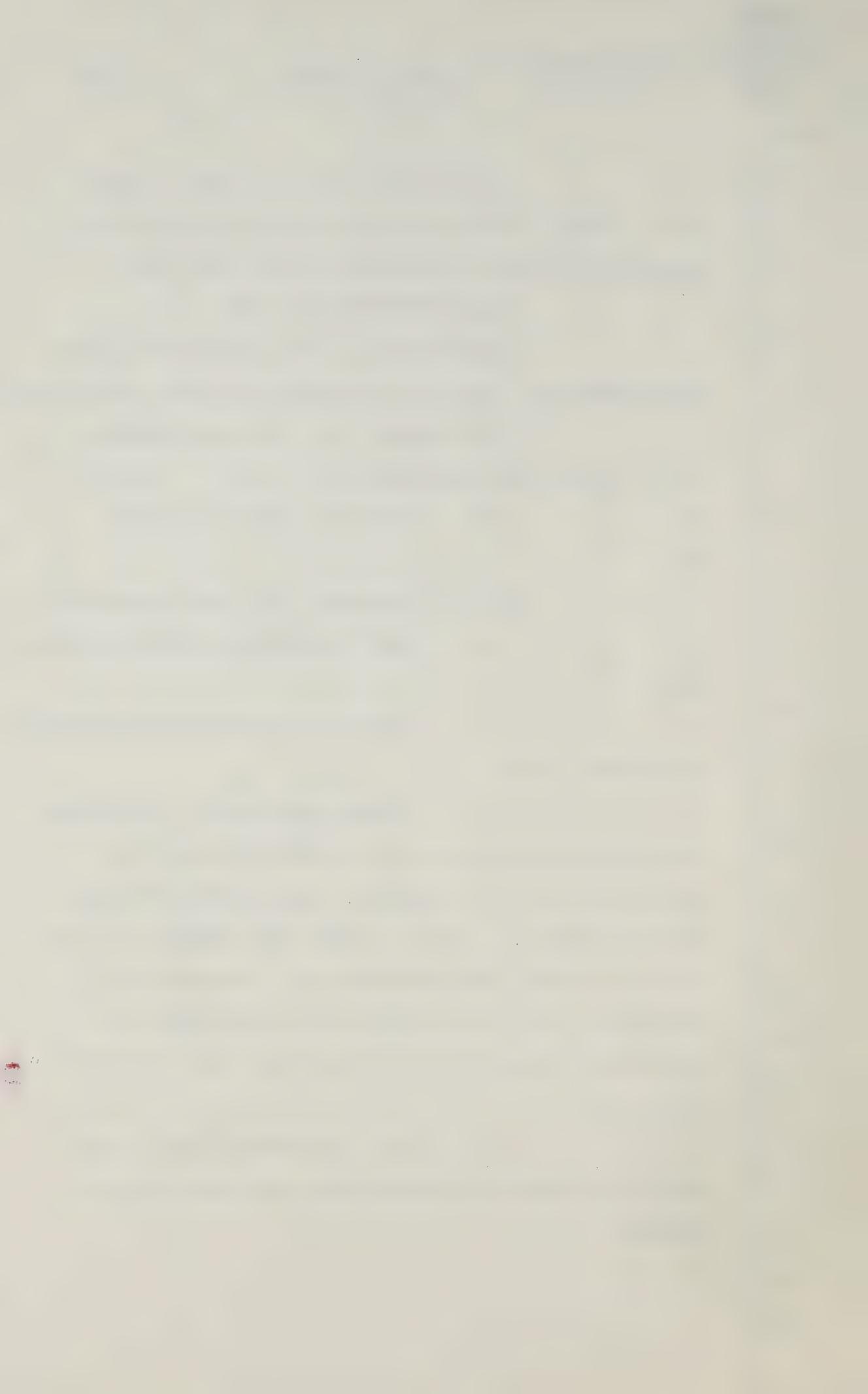
11 Q. How about the drug propanolol?

12 A. Yes, I'm familiar with the drug,
13 yes.

14 Q. Would that test tell you anything
15 about that drug?

16 A. I'm not sure now. I'm trying
17 to recall because that was way back two years and
18 this was one of the drugs that we had found in one
19 of the babies. I'm not really sure whether we have
20 tested it under the conditions for the assay for
21 digoxin or not. We may have but I would have to
22 refresh my memory on that. That was, you know, two
23 years ago.

24 Q. Well, can you do that so you
25 would be prepared to answer the question next time
around?





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2 A. Yes.

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4 Q. And then, sir, I'm just turning
to the HPLC test for a moment. When did you start the
HPLC tests?

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6 A. When we started to develop it
or when we started to apply it or what exactly do you
7 mean?

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Q. Well, why don't you answer both
questions. When did you start to develop it and when
did you start to apply it?

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A. Well, again, I would have to
consult exactly, you know, if you want a month and so
on, the exact month and date, I would have to consult
the experimental notes, if they are still available,
because it was, as I recall it, we began to apply the
HPLC test some time in September, 1981.

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Q. September, 1981?

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A. Yes, that's as I can recall it.

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Q. Would you be good enough to
check your notes so that you would be prepared next
time to give us a more precise answer.

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A. Okay. This date, as I recall
it, was the beginning of the application, so, the
development work would have been done before that
time.

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III10 Q. Yes. You began to develop the test earlier, but then you began to apply it, in your recollection, in September, but you are going to find out for us so you will know?

A. Yes.

Q. Tell us why did you start applying it?

A. Why?

Q. Yes, why?

A. Because it is pretty well standard procedure in Forensic Toxicology to try to have at least two or more different tests for the identification of a drug.

Q. Well, did you do that because it is standard procedure?

A. Well, perhaps standard is the wrong word, but it is a recognized procedure to try to use different tests.

Q. And would I be safe in characterizing the HPLC test as a standard test, it is a well known, well used test?

A. Well, with respect to the digoxin application and blood, I think, as I recall it from the literature, there were, at the beginning of the applications and beginning in the late 1970s,



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III12 2 even though we were working very heavily on the
3 development and the evalation. But it just took
4 the time to satisfy me that we were ready to begin
5 using it.

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Q. And this was a business you
6 had to get ahead with, wasn't it?

7

A. Pardon me?

8

Q. This was a business you had
9 to get ahead with, people wanted to know about these
10 tests?

11

A. Serious investigation, that's
right.

12

Q. Now, just from that business
13 of the tests and the time it takes, I think you said
14 to Mr. Lamek that it would take about a day and a
15 half to two days to do a test, to do the RIA test.
16 You could do several tests at once, but it didn't
17 matter whether you were doing one, didn't matter whether
18 you were doing 10, it's going to take you, you said,
19 from a day and a half to two days you would be comfort-
able with, I think that's what you said this morning.

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A. I said it would take roughly
21 that amount of time to process approximately 10 samples,
22 that's right, yes.

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Q. And would not measureably

decrease the time if you are only doing one sample because there are a number of stages that you have to go through, is that not right?

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A. You still have to go through the same steps, multiple steps and wait a certain time before you proceed from one step to the other step.

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Q. Yes, that's right and one and a half days to two days, that is the comfortable range. That is what you said this morning.

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A. As available to blood samples and as I say different samples require longer than that.

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Q. Tissue samples take longer than that.

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A. Yes.

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Q. How long do they take?

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A. Well, I think there are certain extra procedures that need to be done with tissues such as the breaking -- the initial breaking down of the tissues and the homogenization of the tissues and so it would take somewhat longer time. I don't know what type of estimate. This is an approximation in any case because it depends somewhat on the

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equipment, how it is available and how it is functioning and what needs to be done and so on so that these are approximations. It would perhaps take a day and for 10 samples it may take - and I think I will leave it would take longer.

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Q. Well, let me put this question to you. In respect of the blood samples or in respect of the tissue samples, did you ever do tests in less than a day and a half, or do you know?

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A. Well, we may have. I have done so many tests it's hard to recall the time but we may have. We may have had to work at night, yes.

15

Q. Sure. Do you have any records of that?

16

A. I don't know whether there are any records of that.

17

Q. Would you be good enough to look?
A. I will try to look. If we have managed to complete an RIA before one and a half days. Is that your question, sir?

18

Q. Yes.

19

MR. LAMEK: Mr. Commissioner, the man obviously has undertaken to provide this but for the life of me the relevancy escapes me.

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THE COMMISSIONER: I have some

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difficulty also. What difference does it make? If this is vital to your case. I don't see what difference it would make whether it is faster or slower.

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MR. BOGART: Well, Mr. Commissioner, I am not sure that I can say with confidence what the significance of it is. I notice Mr. Scott was able to have records produced without having to meet any tests.

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THE COMMISSIONER: If it's relevant there is no problem.

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MR. BOGART: I think the relevance of that, sir, is --

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THE COMMISSIONER: Remember what you are asking is it is unlikely he will have a record of it. He may have. If we are going to put him to a great deal of effort I will have to make sure it is relevant before he does.

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MR. BOGART: Well, first of all, sir, if he doesn't have records he can simply say that.

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THE COMMISSIONER: He has to search

for them.

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MR. BOGART: Yes, that is true but beyond this, sir, I think the relevance of this may be he has told us that in order to do these tests



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properly it takes a certain amount of time because you have to go from one stage to the next stage to the next stage and this takes a certain amount of time. If he has done those tests in less than that amount of time then one might wonder about the methodology used with respect to those particular tests and would wonder about it.

THE COMMISSIONER: You mean whether they were done accurately?

MR. BOGART: Yes, I guess one might.

THE COMMISSIONER: All right. Well, I think we had an answer a moment ago. Perhaps you can make what you can make of the fact that is so. That is what you suggested. I don't know. It may have taken some of them less time and it may have taken more.

MR. BOGART: Yes, I guess that is certainly what I was wondering about.

THE COMMISSIONER: I think that's enough but if you can satisfy me at some later time it's important because you may produce this evidence from one of the Commission's witnesses or somebody else if you really need to ask instead of one and a half or two days you need a week, and you may adduce evidence that it's only four or five days.



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Mr. Cimbura is coming back and you
can pursue the matter further.

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MR. BOGART: Well very well, sir.

4

I will leave the matter as it rests for the moment.

5

Q. Now, this morning, Mr. Cimbura,
Mr. Lamek asked you some questions, I believe, about
the work done by Dr. Seccombe of the University of
British Columbia at the Shaughnessy Hospital. Do
you recall that?

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A. Well, that's an article published
in the New England Journal of Medicine.

8

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Q. That is right. That is Volume
308 of the New England Journal of Medicine?

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A. Yes.

11

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Q. And you are familiar with the
article and what it states?

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A. I have seen the article before.

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Q. Well, when Mr. Lamek was asking
you about the background readings that Dr. Seccombe
turns his attention to and the level of therapeutic
dose, I believe Mr. Lamek put a question to you that
suggested that if one took the therapeutic dose
at 4 and one took the background reading at 4, which
is the highest reading that Dr. Seccombe found
approximately that would add together to get 8 and

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he suggested to you that in fact you might be adding
readings of 8 and nevertheless be within a therapeutic
range.

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Do you recall that? You take the
therapeutic range at 4 and Dr. Seccombe's range at
4 and you add them together and that gives you 8.

6

A. Yes, I recall that type of
question.

7

Q. I think you suggested that you
were not happy with those figures.

8

A. What figures?

9

Q. 8.

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A. No, I mentioned that I believe
that if I received a result by my technique of 8
nanograms per millilitre my first concern would be
about possible toxicity resulting from that level.

11

Q. You also I think did a study of
your own, did you not, which lead you have to some
confidence in the fact that a reading of 8 would not
be obtained in this manner.

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A. That is correct. I have done
a study of my own and the results of that study did
not confirm the results obtained in Vancouver.

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Q. Can you tell us when you did
these studies?

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A. Again I cannot recall the approximate time because this was an ongoing study for some time.

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Q. When did you start it?

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A. I can't recall the exact date.

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Q. Can you --

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A. I can look it up.

9

Q. And let us know?

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A. And let you know, that's right.

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THE COMMISSIONER: Did you do a study with Seccombe's research in mind or is this just your general studies and observations?

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THE WITNESS: No. This was before the study came out actually.

13

THE COMMISSIONER: Before you promise to give him something you should consider what you can do. I don't think you can do it unless you did something with Seccombe in mind.

14

Did you do something with Seccombe in mind, with his studies in mind or his organization's studies in mind?

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THE WITNESS: Perhaps I am not understanding the question but my study regarding the background levels in young children was done - started some time as I recall in 1981 and was finished

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well before Dr. Seccombe's.

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THE COMMISSIONER: I seem to be
taking over but you will have the last word in any
event.

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MR. BOGART: Thank you.

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THE COMMISSIONER: Did you do any
specific study along the lines that, let us say,
of the Seccombe search, along that sort of line as
to the presence of digoxin where there is no
therapeutic dosage?

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THE WITNESS: Well, the reason why
I done the study was to - as part of my overall
evaluation of the procedure that we used to let me
know in blood from children that were not receiving
digoxin to let me -- to permit to me to evaluate
our technique whether --

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THE COMMISSIONER: Have you got any
notes with respect to that, that particular study?

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THE WITNESS: Yes.

THE COMMISSIONER: If you have them
you will produce them?

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THE WITNESS: That is right.

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THE COMMISSIONER: Does that solve
your problem?

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MR. BOGART: Yes, Mr. Commissioner.

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Q. And then, Mr. Cimbura, just one more question. You said I think this morning that the RIA test was designed particularly --

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A. Sorry.

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Q. That RIA test was designed particularly for post mortem analysis.

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MR. LAMEK: I don't recall the witness having said that.

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THE COMMISSIONER: I think he said that is why he did it. I don't know he said it was designed. In any event, we can always ask him.

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Was it designed particular for post mortem analysis?

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THE WITNESS: The RIA assay was available more usually for analysis of serum and samples that we want to measure with the work that the RIA has been reported on in the literature.

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MR. BOGART: Q. Was that post mortems particularly or not?

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A. No, this was pre-mortem usually. While there were some applications of the RIA to post mortem, these were much fewer than the literature on ante mortem samples and also there was really no literature, no experience on the application of the RIA to some of the unique



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specimens we received in this investigation such
as tissues fixed in various chemicals and so on
so that my aim was to evaluate the RIA technique
with the eventual application to these different
types of specimens.

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MR. BOGART: I see. Thank you
very much, sir.

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THE COMMISSIONER: Mr. Strathy,
how long would you think you will be?

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MR. STRATHY: Well, Mr. Commissioner,
I think I would be at least half an hour.

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THE COMMISSIONER: Well, I think
we will postpone that until tomorrow if that's
satisfactory to you?

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MR. STRATHY: Yes. I think
Mr. Cimbura has had a long day, as we have all had.

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MR. LAMEK: Mr. Commissioner, now
that we have had a half a day of cross-examination,
I wonder if I could repeat the question that I
asked at lunch time, whether other counsel are able
to tell me whether they propose to cross-examine
tomorrow Mr. Cimbura?

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Mr. Commissioner, perhaps other
counsel can indicate their time in the light of what
has gone before.

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THE COMMISSIONER: Mr. Strathy

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says half an hour. What about you, Mr. Marshall?
Can you help us?

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MR. MARSHALL: I am so impressed
with this witness, Mr. Commissioner, it is highly
unlikely I will doing any cross-examination at all
at this time.

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THE COMMISSIONER: All right.

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Mr. Buhr, have you any thoughts?

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MR. BUHR: I think if I cross-examine
at all I will be very brief.

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THE COMMISSIONER: Miss Symes?

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MS. GOODMAN: I expect to be --

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THE COMMISSIONER: I am sorry,
Miss Goodman. How long will you be?

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MS. GOODMAN: Mr. Commissioner, I
will be a short period.

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THE COMMISSIONER: What is a short
period?

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MS. GOODMAN: Only about five minutes.

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THE COMMISSIONER: Miss Symes?

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MS. SYMES: Between 5 and 10 minutes.

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2 THE COMMISSIONER: Yes, all right.

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Are you keeping track of all this?

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MR. LAMEK: Roughly, Mr. Commissioner.

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THE COMMISSIONER: Mr. Young?

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MR. YOUNG: At this point I only have a few questions. I expect I will be no more than five minutes.

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THE COMMISSIONER: Yes. Mr. Ortved, you don't get a second crack at it.

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Mr. Manning?

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MR. MANNING: About half an hour.

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MR. TOBIAS: Mr. Commissioner, I would think approximately 15 minutes.

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MR. SHANAHAN: Being at the end, Mr. Commissioner, I will find it hard to find a question to ask.

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THE COMMISSIONER: Mr. Olah?

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MR. OLAH: I think I would be in a more difficult situation than my friend being at the tail end.

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THE COMMISSIONER: It looks like tomorrow morning.

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MR. LAMEK: It looks like tomorrow morning to me too.

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THE COMMISSIONER: Yes, Mr. Manning?

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MR. MANNING: Mr. Commissioner,

before we adjourn for the day, I was delighted this morning when I walked in to find a copy of the transcript of yesterday's proceedings on my desk.

I was not delighted to find out I was expected to share that one copy with two or three other persons. Now certainly the objective that was established a long time ago, an objective that was sought and we have really gone a long way towards reaching, namely co-operation amongst the people who represent the parents. It is quite a difficult situation for us to read that transcript together and I would ask that each --

THE COMMISSIONER: The transcript, does it come in one copy?

MR. MANNING: We only had one copy.

THE COMMISSIONER: I understand you only had one copy, and I think that was - I suppose that was based upon what I understood to be the co-operation amongst counsel for the parents.

MR. MANNING: Co-operation with respect to background material and co-operation with respect to one copy of transcript --

THE COMMISSIONER: This might be better discussed in chambers with the three of you,

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2 do you not think, because this is a question of
3 funding, and I don't know, unless you want to
4 discuss it I will happily discuss it outside.

5 MR. MANNING: I don't see any
6 reason why we can't discuss it.

7 THE COMMISSIONER: Well, the only
8 reason - all I can take from you is that you want
9 to have three copies instead of one copy.

10 MR. MANNING: Exactly.

11 THE COMMISSIONER: And all I can
12 answer to that is that is money. That is going to
13 be additional costs. I don't know how much it is,
14 and Mr. Chapman has disappeared. I don't know how
15 much it is, but that is the objection. That is
16 the only objection that you are faced with is the
17 amount of money that is involved. I had hoped that
18 there would be co-operation among the counsel for
19 the --

20 MR. MANNING: We are.

21 THE COMMISSIONER: So that you
22 would just need one copy. You tell me you can't
23 get along with one copy.

24 MR. MANNING: We can't get along
25 with one copy of the running transcript. We were
discussing the preliminary hearing frankly, which



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has already created a problem in the past.

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THE COMMISSIONER: Well, I don't see how it could. 40 volumes, nobody can be reading 40 volumes at one time so that that can't be a problem that is legitimate.

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MR. MANNING: The running transcript is a problem because we get it in the morning and if, for example, I am not here and Mr. Labow is here in my place and I will want to read that transcript at night, and if Mr. Tobias is not here he will want to read it.

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THE COMMISSIONER: I will take it up with Mr. Chapman and I will find out what the costs are and I may see you tomorrow.

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MR. MANNING: All right.

THE COMMISSIONER: At any rate you won't have a transcript of today's proceedings until at the earliest 9 o'clock. And tonight did you all intend to be burning the midnight oil from 9:30 on tonight?

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MR. MANNING: Not with respect to today's proceedings. Today is no problem.

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THE COMMISSIONER: Well, perhaps Mr. Tobias or Mr. Shanahan, you could have that privilege then.



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MR. TOBIAS: I am afraid I have
a previous commitment this evening, Mr. Commissioner.

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THE COMMISSIONER: Well, I don't
think this is an immediate problem, Mr. Manning,
and we will work on it and see if we can find the
solution.

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Anything else? Yes. All right,
then until 10 o'clock tomorrow morning.

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--Whereupon the hearing adjourned at 4:30 p.m.
until Thursday, June 23rd, 1983 at 10:00 p.m.

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